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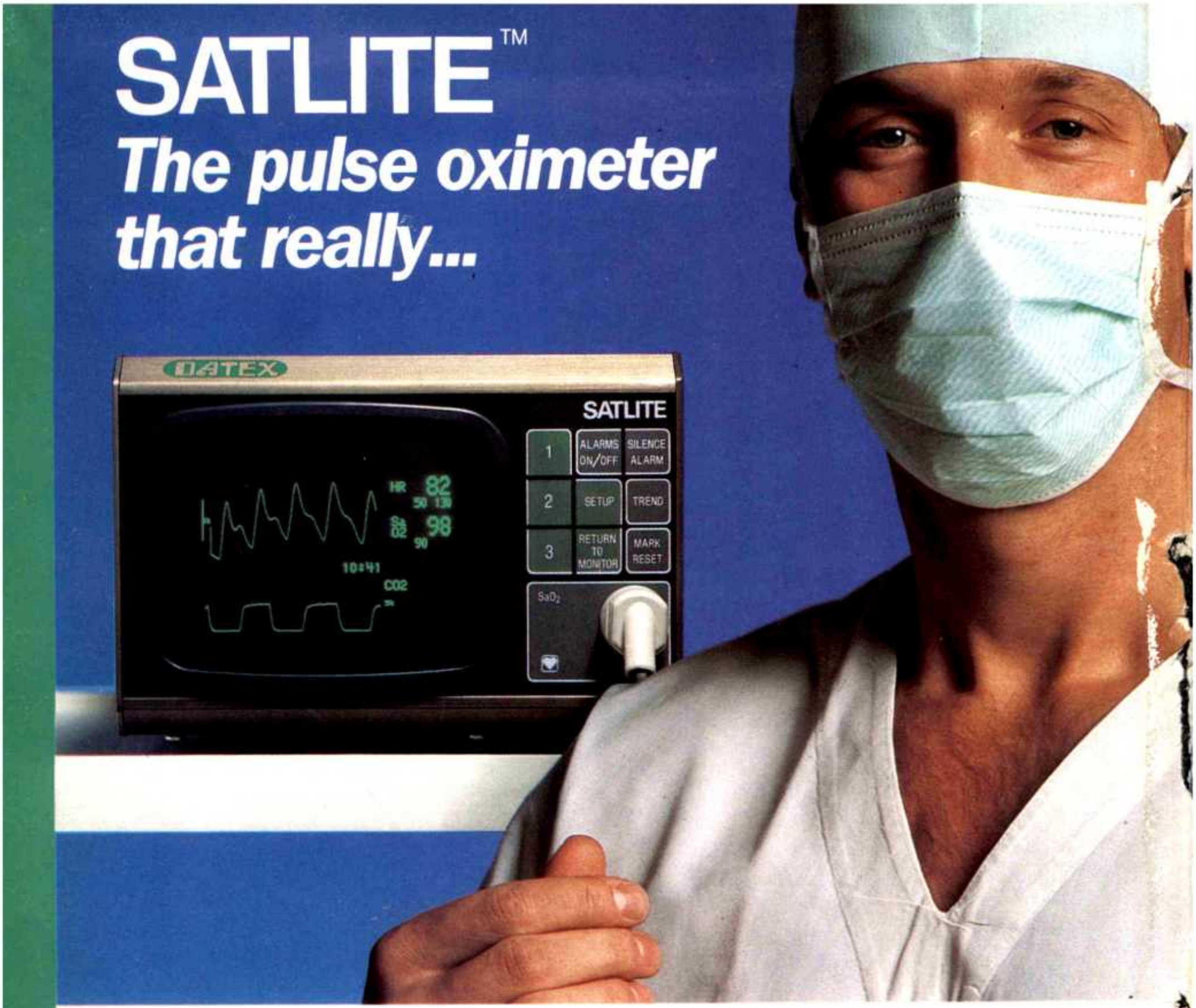

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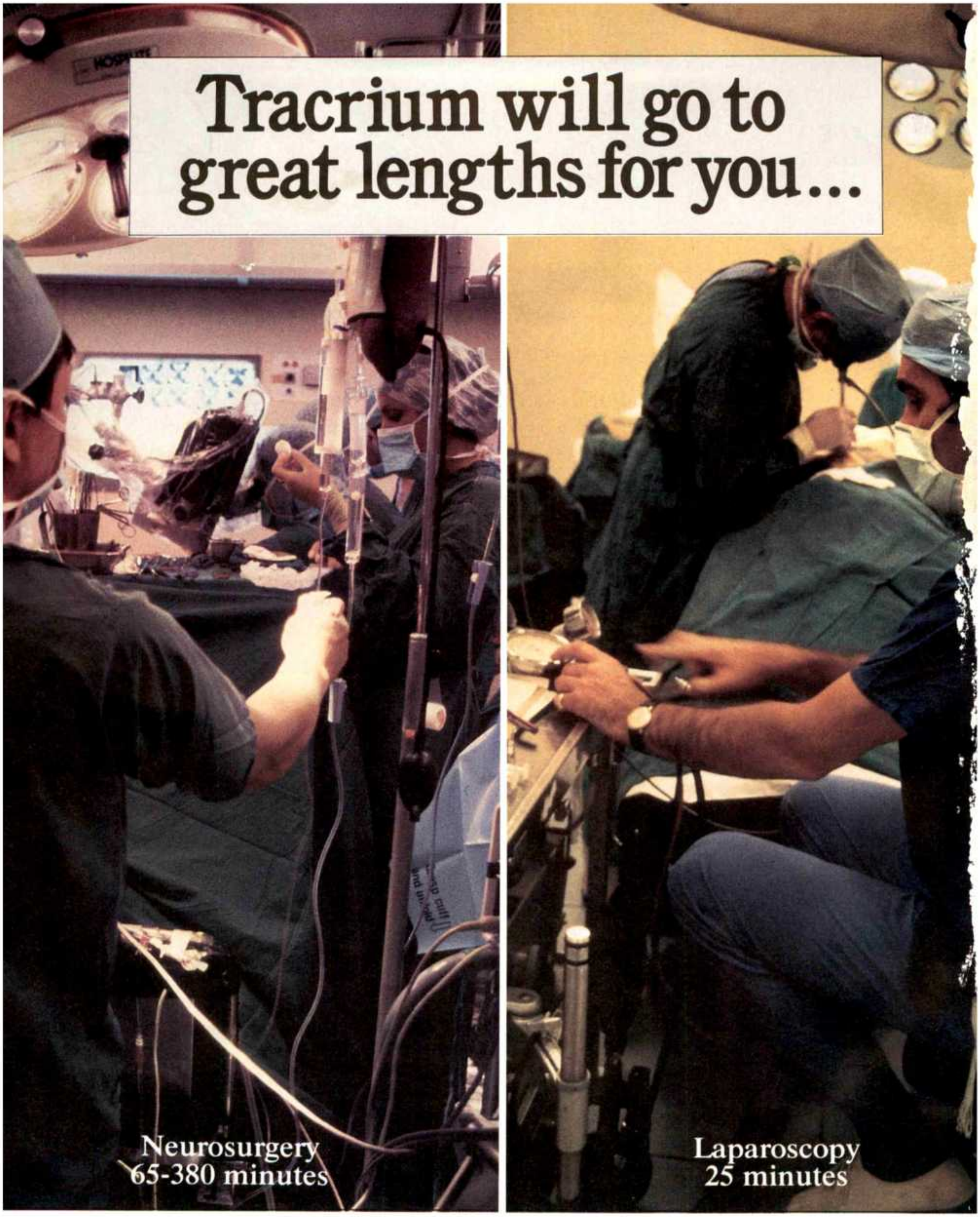
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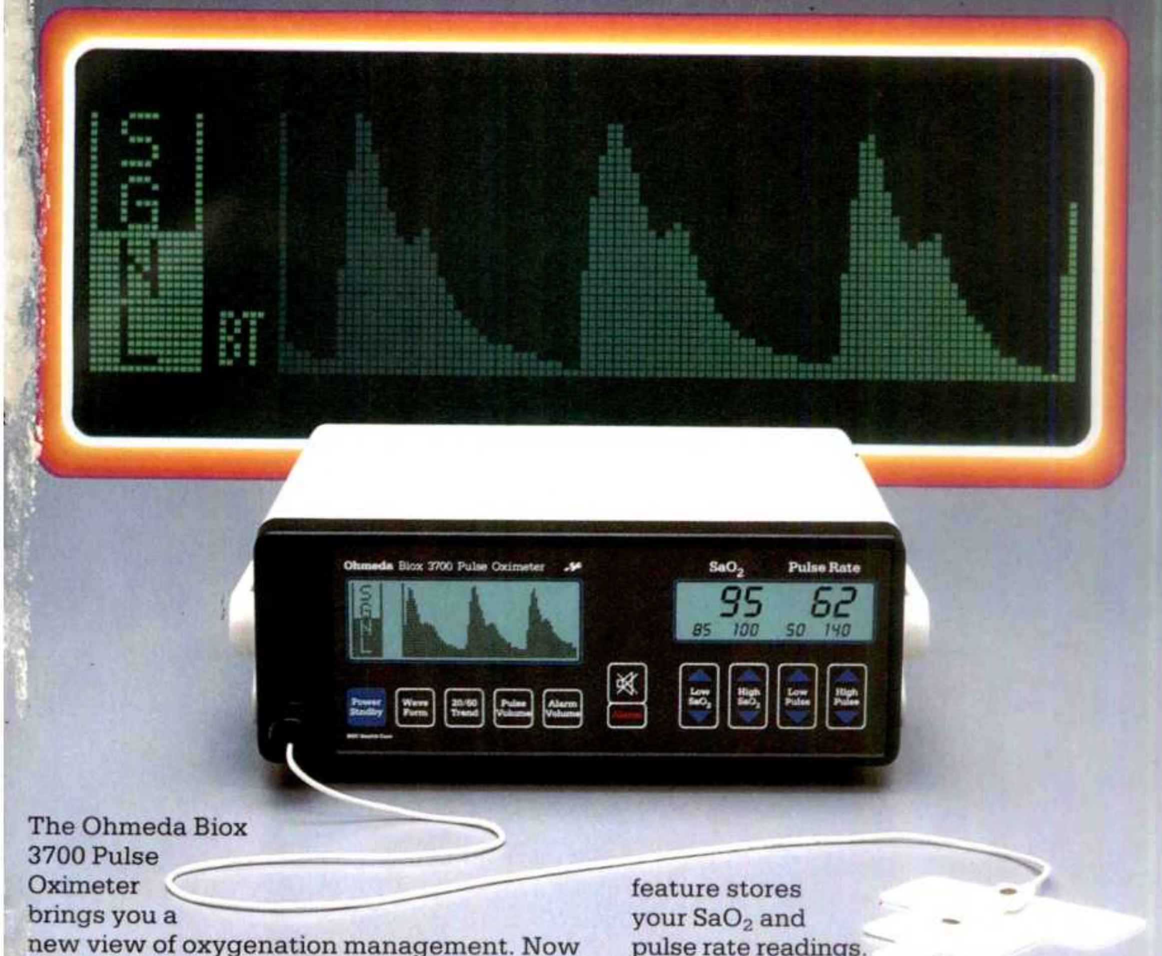

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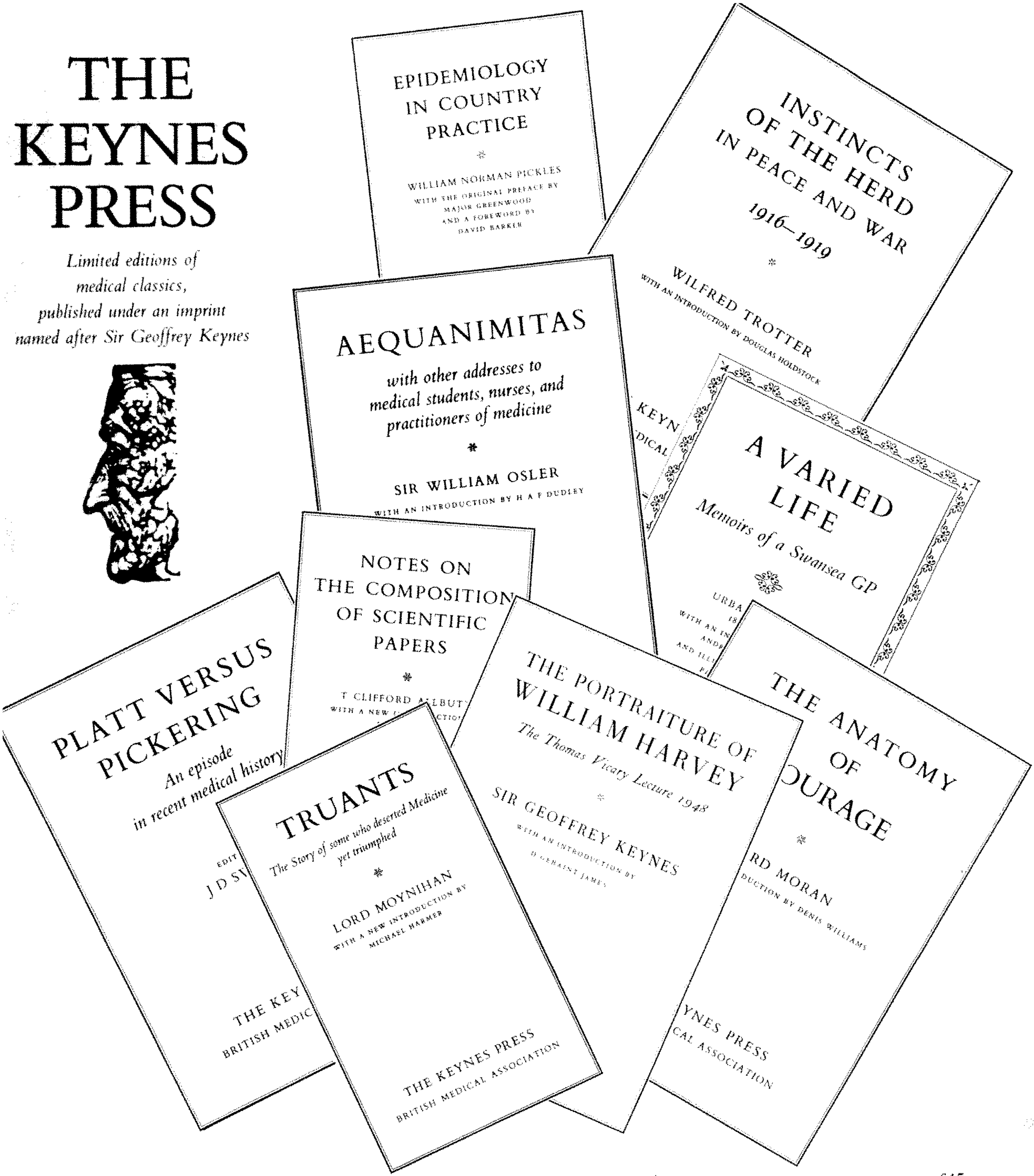
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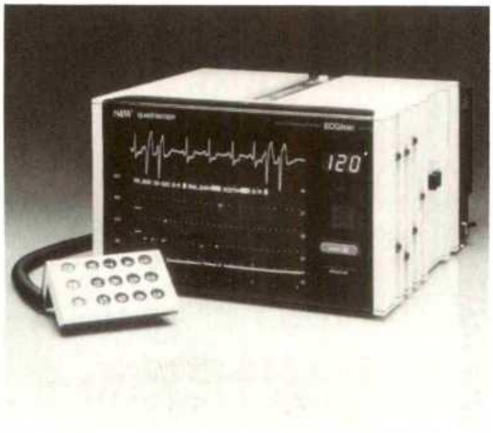

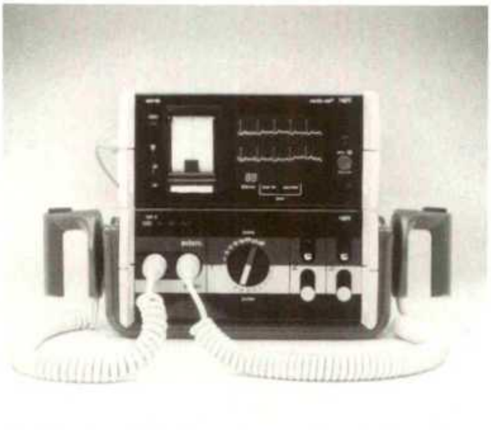

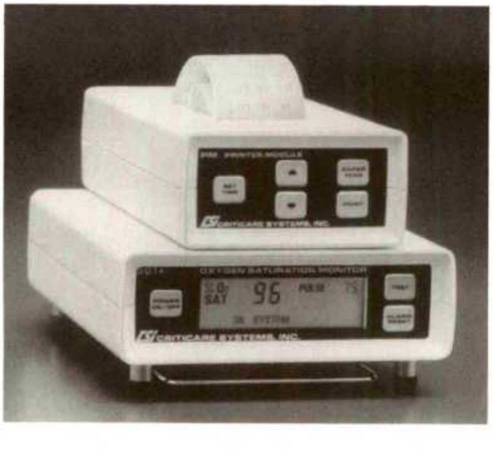

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1. Feldman SA; Clinical Experiences with Norcuron, Excerpta Medica (1983) 199-200
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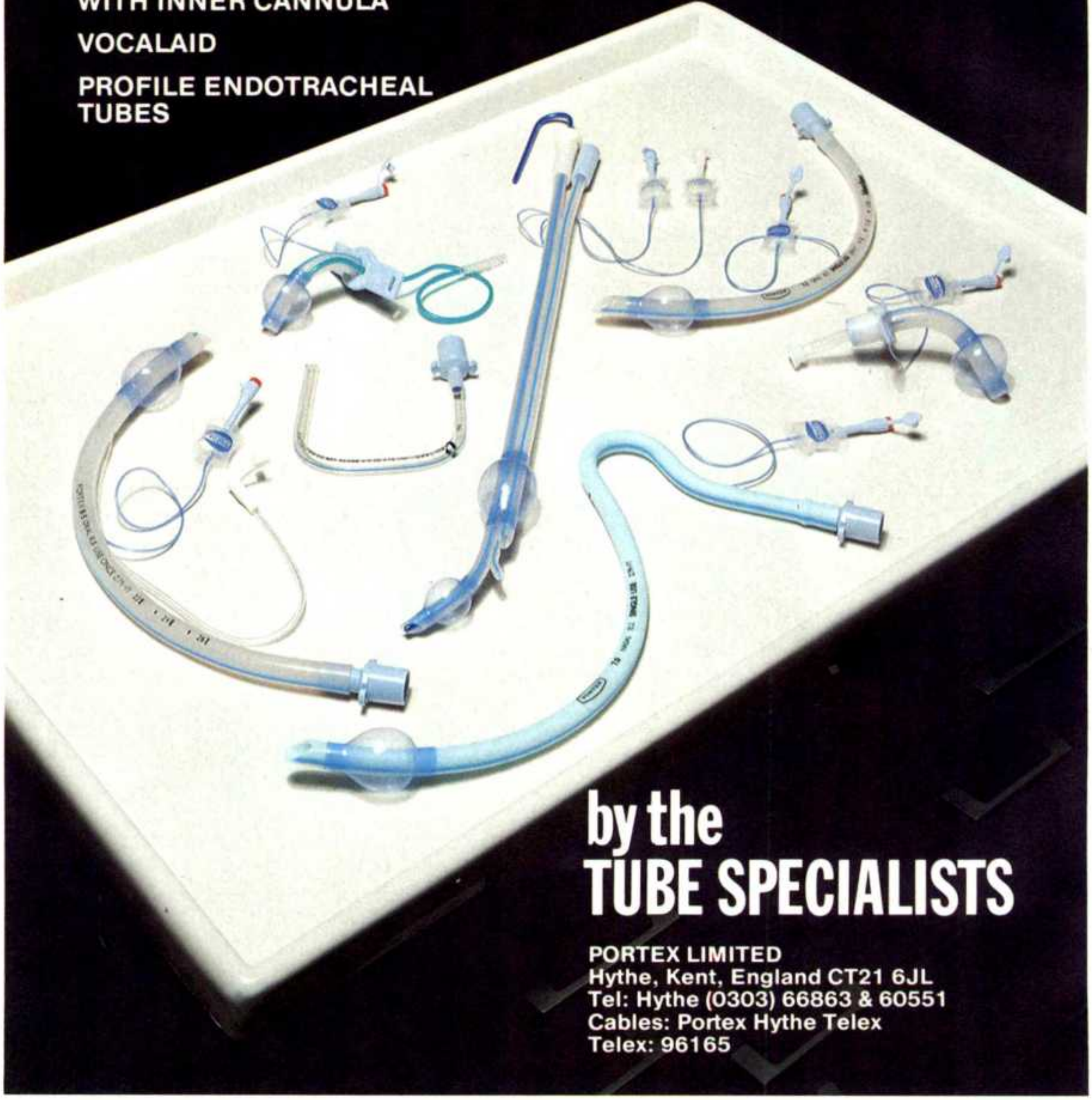

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 59, No. 4 APRIL 1987

EDITORIAL

INTRATHECAL OR EXTRADURAL: WHICH APPROACH FOR SURGERY?

Traditional teaching presents the anaesthetist with some fairly standard attitudes to guide his choice between the intrathecal and extradural approaches to spinal anaesthesia. The intrathecal technique is usually described as easier to learn, quicker to perform, clearer in the endpoint of successful needle positioning, more rapid in onset and more controllable in its spread than extradural blockade. It requires a smaller dose of local anaesthetic, yet will produce a profound degree of blockade which is more consistent in its distribution—"missed" segments (as distinct from inadequate spread) being very rare after intrathecal injection. For these reasons, the intrathecal approach is usually preferred for a single injection technique, and the extradural when a catheter is needed to prolong blockade into the postoperative period.

However, the intrathecal method has some disadvantages which the extradural does not. The most discussed is the headache that can occur after dural puncture, particularly in the young, pregnant female. Careful technique can minimize its incidence, but nobody should use intrathecal blockade if they cannot deal with this complication. Since extradural blood patch is now the definitive treatment, the modern anaesthetist must be skilled in both techniques. If this is the case, why is extradural blockade not preferred more often for a single injection technique?

The standard arguments have been presented, but do they stand up to critical analysis? The actual process of extradural needle insertion should take no longer than lumbar puncture. Indeed, the delay while the free flow of cerebrospinal fluid through a fine-gauge needle is confirmed may make the latter technique slower. It is the subsequent insertion of a catheter, with appropriate verification of its position, that delays extradural block. If a catheter is not inserted, time is saved and the risks of the two dreaded complications of extradural blockade (i.v. and intrathecal injection of a large dose of local anaesthetic) are almost nil. Catheters also seem to be more associated with the development of unilateral blockade than are single injections.

What of the time course of the block? A rapid onset after extradural injection may be obtained by using 2% lignocaine with adrenaline, but its duration may be inadequate for a number of common surgical procedures. Bupivacaine 0.5% will give a longer duration, but the use of this solution is probably responsible for the reputation that extradural block has for being slow and "patchy" in onset. The relatively recent availability of 0.75% bupivacaine overcomes this problem and can produce an extradural block that is almost as rapid in onset as intrathecal techniques. The injection of up to 15 ml at low lumbar level produces very reliable conditions for lower limb surgery in a short period of time—especially if the anaesthetist is prepared to supplement the block with light sedation. Analgesia persists for several hours, generally for longer than it does after intrathecal block.

Many anaesthetists seem reluctant to use the concentrated solution of bupivacaine because of the reports of severe systemic reactions after its injection. A number of these cases were in obstetric patients and this led to the inclusion in the data sheet of a warning against the use of this concentration during labour. It would be a brave anaesthetist who used it in that situation at present, although the proscription is quite illogical and merits reconsideration. Used with full awareness that it is a very concentrated solution, 0.75% bupivacaine is no more dangerous than any other local anaesthetic preparation.

One of the great features of extradural blockade is that its distribution can be varied to suit the site of the operation, a point emphasized by Dogliotti in his original description. Intrathecal injection is always performed at low lumbar level, and the concentration of local anaesthetic is greatest in the nerves of the cauda equina. As the solution spreads cranially, so its concentration decreases. Thus, the duration of blockade is shorter in the upper dermatomes and this can produce the distressing situation where a patient who has had an inguinal hernia repaired can have wound pain, but totally blocked legs. Such total paralysis is in fact fairly unusual during extradural blockade with the doses of 0.75% bupivacaine mentioned above. If an extradural injection is performed at the same dermatomal level as that at which the wound is to be made, the greatest concentration of drug will be in the most relevant nerves. The patient becomes aware of pain only when all other features of the block have regressed.

If this "segmental" approach to extradural block is used, it can be very reliable. With intrathecal injection, spread from the lumbar region depends on the properties of the solution injected and the way in which they are manipulated. Ideally, any local anaesthetic prepared for intrathecal use should be available in a range of baricities, or in a form that allows its baricity to be adjusted before injection. In North America, the commercial preparations of amethocaine meet this requirement and its isobaric form will produce good blockade of the legs and perineum with minimal thoracic spread. Currently, this agent is unavailable in the U.K., where the only preparation specifically marketed for intrathecal use is hyperbaric bupivacaine. In the supine patient, this produces a block that is usually far more extensive than is needed for the sort of surgery commonly performed under intrathecal blockade. The only alternatives are the plain solutions of lignocaine and bupivacaine, which are *not* isobaric and cannot be relied upon to produce blockade to the level of the inguinal ligament yet, frequently, (bupivacaine in particular) cause very extensive blockade.

Recent years have seen a great reawakening of interest in intrathecal blockade. In no other way can an anaesthetist obtain so much effect for the injection of so little drug, and for many patients and procedures it is the regional method of choice. The elderly patient in poor general condition who requires amputation of a leg is best served by the production of a profound block with the smallest possible dose of local anaesthetic. Transurethral resection of the prostate needs analgesia of the low thoracic segments to block the discomfort of bladder distension as well as profound blockade of the sacral segments. Again, a properly chosen intrathecal technique is the best way to achieve this. In many other surgical situations, an extradural technique, based on the principles outlined above, can provide all the benefits of intrathecal blockade and also avoid some of its problems. Every time that a spinal anaesthetic is considered for a patient, careful thought should be given as to which is the more appropriate approach to its administration.

J. A. W. Wildsmith

Br. J. Anaesth. (1987), 59, 399–409

EFFECTS OF HALOTHANE, ISOFLURANE AND ENFLURANE ON VENTILATION IN CHILDREN

W. S. WREN, P. ALLEN, A. SYNNOTT, D. O'KEEFFE AND P. O'GRIOFA

SUMMARY

The ventilatory effects of halothane in eight children were compared with those of isoflurane in eight children and enflurane in six children. All studies were completed before surgery commenced, and the children received no preoperative medication. The depression of ventilation produced by the three agents increased in a dose-related fashion as the alveolar concentrations were increased, and the depression of ventilation that they produced in oxygen was greater than that produced by equipotent concentrations in nitrous oxide. While the increase in ventilatory frequency and the decrease in T_E *associated with increasing concentrations of halothane were statistically significant (*$P < 0.05$*), the increase in frequency associated with isoflurane was not, although it was sufficient to maintain the end-tidal and arterialized venous* P_{CO_2} *in the isoflurane group at a value which did not differ significantly from that in the halothane group. Profound depression of ventilation was produced in the children by enflurane, clearly because no increase in ventilatory frequency was associated with its use. It was evident that the ventilatory effects of the three volatile agents in unstimulated children are very similar to those described elsewhere in the adult. There was no difference of any clinical significance between the degree of depression of ventilation produced by halothane and isoflurane in children.*

Although a number of communications have compared the effects of halothane, isoflurane or enflurane on a variety of physiological functions in the adult (Fourcade et al., 1971; Eger, 1981), comparative studies in children have tended to address such limited aspects as the incidence of cardiac arrhythmia (Sigurdsson et al., 1983) and the effects on intraocular pressure (Ausinsch et al., 1975). As there are relatively few data on the effects of these agents on ventilation in children, a controlled study was performed in anaesthetized children before surgery.

PATIENTS AND METHODS

Informed consent was obtained from the parents of the children studied, and the study was approved by the hospital Ethics Committee.

The effects of each agent on ventilation were determined with nitrous oxide (65% alveolar) in oxygen at 1.25, 1.50, and 1.75 MAC, and with oxygen alone at 1.00 and 1.25 MAC, in three groups of children. The details of the children included in the study are described in table I.

The eight normal children in the halothane group ranged in age from 5 to 10 yr (mean 8.9 yr), and in body weight from 20 to 49 kg (mean 28 kg); the eight normal children in the isoflurane group ranged in age from 5 to 9 yr (mean 7.2 yr), and in body weight from 20 to 33 kg (mean 24.7 kg). For reasons described below (Results), the effects of enflurane were studied in six children only, and they ranged in age from 5 to 9 yr (mean 7.4 yr), and in body weight from 18 to 30 kg (mean 23.8 kg). None of the children received any pre-anaesthetic sedation or parasympatholytic drug, and all studies were completed before surgery commenced.

Anaesthesia was induced by inhalation in all patients and tracheal intubation was facilitated with suxamethonium 1–2 mg kg^{-1}. The size of the tracheal tube was chosen on the basis of a

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W. S., WREN, M.B., F.F.A.R.C.S.I., F.F.A.R.C.S.; P. ALLEN, M.B., F.F.A.R.C.S.I.; A. SYNNOTT, M.B., F.F.A.R.C.S.I ; D. O'KEEFFE, M.B., F.F.A.R.C.S.I.; P. O'GRIOFA, B.SC.; Department of Anaesthetics & The Children's Research Centre, Our Lady's Hospital for Sick Children, Dublin, Ireland. Accepted for Publication. May 19, 1986.

TABLE I. *Details of patients studied*

	Sex	Age (yr)	Wt (kg)	Ht (cm)	Tracheal tube i.d. (mm)	$\dot{V}$F (litre min^{-1})
Halothane	M	7.75	23	124	6.0	11.0
	M	10.5	31.5	137	6.5	12.0
	M	9.1	22	130	6.5	11.0
	M	10.16	24	122	6.5	11.0
	M	8.5	26	126	6.5	11.0
	M	5.3	20	118	5.5	9.6
	M	10.16	29	141	6.5	11.0
	F	9.8	49	153	7.0	13.5
Isoflurane	M	6.25	22	115	5.5	11.0
	M	5.16	20	111	5.5	9.6
	M	5.25	20	117	5.5	9.6
	M	9.4	33	132	6.5	12.0
	F	9.8	28	127	6.0	11.0
	M	6.0	20	103	5.5	9.6
	M	7.3	30.5	129	6.5	12.0
	M	8	26	120	6.0	11.0
Enflurane	F	9.16	25	137	6.5	11.0
	M	9.16	30	130	7.0	11.0
	M	6.0	22.5	115	6.0	11.0
	M	8.4	23	125	6.5	11.0
	M	5.3	18	108	5.5	9.6
	M	6.4	24	124	6.0	11.0

standard formula (Steward, 1979), with the usual clinical modification of using a tube size 0.5 mm larger or smaller than the tube indicated by the formula, if that size permitted undue leakage of gas, or proved to be too "snug" fitting. The resistance to gas flow across each tube size with the appropriate connector, and with and without the pneumotachograph attached, was measured in a bench test using a Mercury VP5 ventilator/pump test meter. The values for each tube size, with 65% nitrous oxide in oxygen delivered at the peak inspiratory flows encountered with that size of tube in the course of the study, are presented in table II.

A standard anaesthetic machine (Penlon Ltd), a standard vaporizer (Draeger) and a Bain Co-axial breathing system were used throughout. The fresh gas flow rates ($\dot{V}$F) used were derived by adding to the flows recommended to prevent rebreathing with the Bain system (Steward, 1979) a volume of 600 ml min^{-1} to replace the volume extracted from the breathing system by the three infra-red gas analysers used.

Ten variables were recorded at each MAC value: minute volume ($\dot{V}$E), ventilation rate (f), tidal volume (VT), peak inspiratory flow (VP), mean inspiratory flow ($\dot{V}$I), end-tidal carbon dioxide tension (PE'$_{CO_2}$), inspired carbon dioxide concentration (FI$_{CO_2}$), inspiratory time (TI), expiratory time (TE) and end-expiratory pause time (TP); the ratios of fresh gas flow to minute volume ($\dot{V}$F/$\dot{V}$E) and the inspiratory duty cycle (TI/T^{tot}) were derived.

The alveolar concentrations of the three volatile agents required to achieve each MAC multiple, and the alveolar concentrations (with standard

TABLE II. *Resistance to gas flow (65% nitrous oxide in oxygen) through the tracheal tube sizes used, with and without the pneumotachograph, for the peak inspiratory flows encountered for each tube size in the course of the study. T+C = Tube+connector; T+C+P = tube+connector+pneumotachograph*

Tube size (mm i d.)	Tube length (cm)	Peak flow (litre min^{-1})	Resistance (cm H_2O litre^{-1} min^{-1})	
			T+C	T+C+P
5.5	16	13	0.1	0.177
6.0	17	14.5	0.08	0.157
6.5	18	18	0.08	0.157
7.0	20	13	0.06	0.138

TABLE III. *End-tidal concentrations (mean ± SD) of halothane, isoflurane and enflurane used in the study compared with the alveolar concentrations equivalent to the MAC multiples studied, for children aged 5–10 yr. *MAC 5–10 yr (Eger, E. I.* II, *personal communication)*

	In oxygen				In 65% nitrous oxide in oxygen					
MAC:	1.0* (%)	End-tidal (% used)	1.25 (%)	End-tidal (% used)	1.25 (%)	End-tidal (% used)	1.5 (%)	End-tidal (% used)	1.75 (%)	End-tidal (% used)
Halothane	0.9	0.89 (0.03)	1.125	1.124 (0.02)	0.56	0.58 (0.02)	0.79	0.80 (0.06)	1.01	1.01 (0.02)
Isoflurane	1.38	1.36 (0.06)	1.72	1.75 (0.03)	0.86	0.85 (0.02)	1.21	1.24 (0.02)	1.55	1.57 (0.03)
Enflurane	2.02	1.94 (0.15)	2.53	2.37 (0.22)	1.26	1.41 (0.04)	1.77	1.92 (0.18)		

deviation) actually achieved in the course of the study are detailed in table III.

The alveolar concentrations of the agents were altered in a uniform sequence of progressive increases in concentration from MAC 1.25 to 1.50 and 1.75 with 65% nitrous oxide in oxygen, followed by MAC 1.25 in oxygen. The concentrations were then decreased for the final measurement at MAC 1.00 in oxygen. This procedure, which precludes randomization, was designed to limit the overall time of anaesthesia to the minimum compatible with true equilibration at each MAC value, experience in previous studies having shown that the time to achieve equilibration, when changing from a high to a low alveolar concentration, was considerably longer—in particular with a more soluble agent such as halothane—than that involved at gradually increasing alveolar concentrations. Furthermore, the sequence used mimics the common clinical practice of decreasing the alveolar concentration of the volatile agent in oxygen when ventilatory depression is produced by high concentrations with nitrous oxide.

The first recording, of the data of five sequential breaths, was made when the child had been breathing an alveolar mixture of MAC 1.25/nitrous oxide (in oxygen) for 15 min. At subsequent MAC values equilibration was judged to have taken place when the values of end-tidal vapour concentration (FE'_{vap}), $\dot{V}E$ and VT had been stable for a number of breaths, as portrayed in the computer print-out of the values obtained in an individual patient (table IV).

Equilibration at new alveolar concentrations was frequently accomplished in less than 10 min in the halothane and isoflurane groups; mean equilibration times recorded were 8.89 (1.95) min and 8.48 (1.67) min, respectively. This observation, which was frequently verified throughout the series by comparing the variables at 5 min and 15 min of equilibration, is in accordance with the observation that equilibration may be accomplished in considerably less than 15 min (Eger, 1974). Equilibration with enflurane presented extreme difficulty, as discussed below (Discussion). When equilibration was established at each MAC multiple, and VT, $\dot{V}E$ and PE'_{CO_2} were stable, the data from five sequential breaths were recorded and blood-gas tensions measured on arterialized venous samples (France, Eger and Bendixen, 1974) withdrawn from an indwelling Teflon cannula in a vein in the dorsum of the hand. The mean value (SD) for each variable, with each agent, at each MAC was derived from the added data of all the recorded breaths at that MAC value, of all of the children studied with the particular agent.

Ventilatory pattern and gas analysis

The equipment and calibration procedures for the measurement of ventilatory flows and volumes and the gas analysers have been described (Wren et al., 1984). Inspired gas flow was measured with a Fleisch II heated pneumotachograph which was connected to a differential pressure transducer (Mercury VP5). Airway pressure was measured using a separate pressure transducer (Mercury VP5). To obviate error resulting from electronic drift, this instrument was reset before each study and automatically reset its recordings, by opening to atmosphere, to record true zero values at preset intervals; in addition, the computer program used opened the instrument to atmosphere at intervals of 6 min and each time the main menu was accessed, or a file was saved to disc.

The pneumotachograph was inserted between the swivel mount on the tracheal tube and the coaxial hose of the Bain breathing system (fig. 1).

The concentrations of nitrous oxide, carbon dioxide and the volatile agent in use were measured continuously by three infra-red gas

TABLE IV. *Computer print-out of end-tidal vapour concentrations* ($F\acute{E}'_{vap}$), V_T *and* $\dot{V}_E$ *of the breaths recorded from a 9.8-yr old 28-kg girl during the isoflurane study. The equilibration times for the successive changes in MAC multiples are 7 min 57 s, 21 min 25 s and 9 min 49 s, respectively.* **Breaths during which arterialized venous samples for carbon dioxide tension were taken*

	No.	Time	$F\acute{E}'_{vap}$ (%)	V_T (ml)	$\dot{V}_E$ (ml min^{-1})
MAC 1.25/N_2O	1	14.47.06	0.8871	91.88	3150
	2	14.47.22	0.8906	96.26	3377
	3	14.47.39	0.8671	91.88	3132
	*4	14.48.5	0.8906	91.88	3301
	*5	14.49.47	0.8671	74.38	2594
	6	14.51.29	0.9140	112.9	3682
	7	14.51.58	0.8671	87.08	3286
MAC 1.5/N_2O	8	14.58.55	1.265	69.49	2496
	9	14.59.24	1.242	69.32	2475
	10	14.59.5	1.265	73.65	2728
	11	15.00.11	1.265	73.65	2554
	12	15.01.06	1.289	65.15	2538
	*13	15.01.06	1.289	65.15	2538
	*14	15.01.54	1.289	60.66	2179
	15	15.02.4	1.289	69.32	2310
	16	15.03.07	1.312	64.99	2532
MAC 1.75/N_2O	17	15.09.06	1.593	47.42	1714
	18	15.09.23	1.570	47.42	1767
	19	15.09.44	1.546	47.42	1812
	*20	15.10.39	1.546	47.42	1778
	*21	15.11.28	1.523	51.73	1928
	22	15.12.44	1.523	47.42	1789
	23	15.13.2	1.523	51.73	1773
MAC 1.25/O_2	24	15.33.45	1.734	55.31	1774
	25	15.34.02	1.781	44.94	1361
	26	15.34.25	1.687	48.39	1481
	27	15.34.42	1.757	44.94	1506
	*28	15.35.2	1.710	51.85	1637
	*29	15.36.07	2.976	55.31	1659
	30	15.37.05	1.757	41.48	1232
	31	15.38.21	1.687	51.85	1525
MAC 1.0/O_2	32	15.47.1	1.359	68.92	2007
	33	15.47.42	1.382	79.26	2191
	34	15.48.06	1.359	72.37	1779
	35	15.48.29	1.382	68.92	1821
	*36	15.50.16	1.382	86.15	2237
	*37	15.51.36	1.382	79.26	1998
	38	15.52.27	1.382	62.03	1780
	39	15.52.55	1.007	86.15	2218

analysers (Beckman LB II). The accuracy of the infra-red analysers across a range of ventilatory frequencies was assessed by a bench test (Synnott and Wren, 1986) which confirmed that these instruments were accurate at frequencies of up to 30 b.p.m.; at 37 b.p.m. the instrument developed a 5 % error, by which inspired concentrations were underestimated and end-tidal concentrations overestimated. Thus, for example, if the instrument displayed an end-tidal value of 1 % at a frequency of 37 b.p.m., the true value was 0.95 %. The added deadspace of the flow head and analyser connections, measured by water displacement, was 10 ml.

Computer analysis and recording of data

The data from the pneumotachograph and gas analysers were fed into a computer (Apple II) via a high speed analog-to-digital converter (Mountain Computer). During each sampling cycle the computer scanned all analog imputs at a high sampling rate (up to 100 samples s^{-1} per channel) and the sampling method catered for the real time delay of the gas analysers, which repeatedly

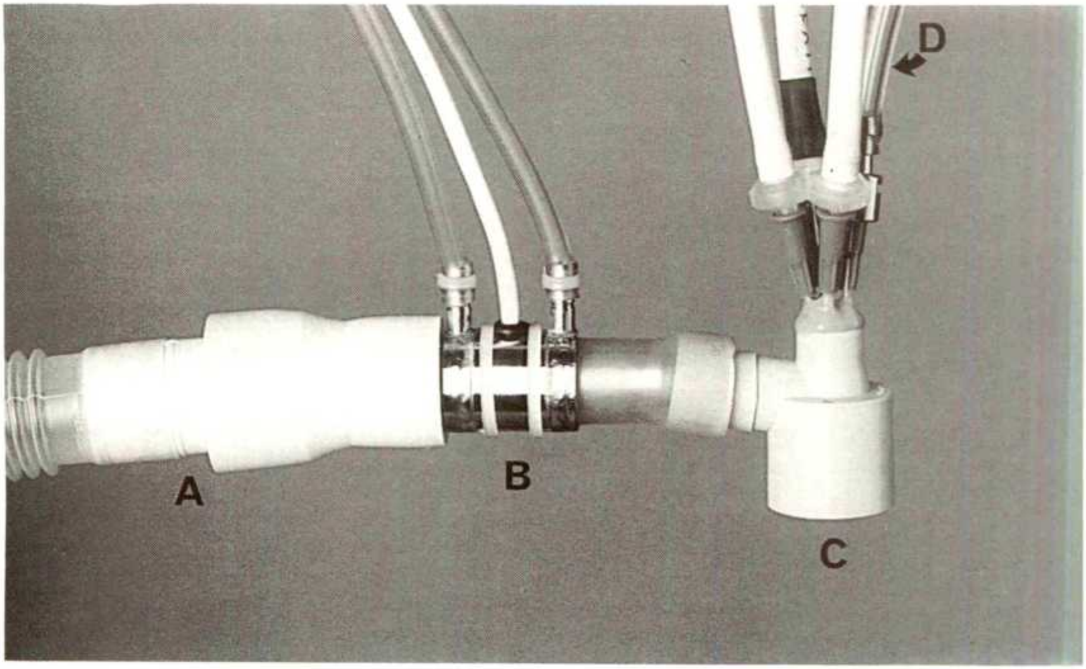

FIG. 1. The pneumotachograph (B) was inserted between the swivel mount of the tracheal tube (C) and the coaxial hose of the Bain breathing system (A). The swivel mount was modified to accommodate the airway pressure probe (D) and the sampling tubes of the three infra-red gas analysers.

measured 220 ms, when gas mixtures were aspirated at 200 ml min^{-1}.

The computer program identified, recorded and displayed graphically valid breaths in real time, and contained a number of mechanisms for identifying the beginning and the end of inspiration and expiration, to ensure accurate recording of the timing components of ventilation. In the principal method used, the computer first defined a time window the duration of which was 10% of full time scale, and the end-point of which was when the volume recorded was at least 7% of the full volume scale. The computer scanned the window from beginning to end, found the slope of the flow signal at +5% of full scale deviation, and projected the flow curve based on this slope backwards to zero crossing, which was the beginning of inspiration. Similar algorithms were applied to the definition of the end of inspiration, expiration and pause time.

The program took account of the effect of the 600 ml min^{-1} aspirated by the three infra-red analysers and corrected the values accordingly and, also in real time, applied all of the factors necessary to correct for errors resulting from temperature difference and changes in the viscosity of the gas mixture, electronic drift in the analysers and the effects of spectral overlap and "collision broadening".

A subsidiary program facilitated the calibration of the analysers and pneumotachograph, making this process easier and more accurate. This program also recorded a file with patient data which had two functions: it modified the correction factors so as to compensate for any slight miscalibration, and provided a permanent record of the accuracy and linearity of the analysers and pneumotachograph, which could be scrutinized at a later date should there be doubt about the validity of any recorded data.

The computer program also produced a composite file of corrected data (in addition to a raw file). This composite file was formatted in such a way that it could be readily transferred, via the RS 232 interface of the Apple, to another computer which ran a CP/M operating system (BBC Microcomputer with Z80 second processor). Once in this CP/M environment, all necessary numerical manipulations and statistical analyses were performed rapidly and accurately using a commercial statistical programme (Microstat, Ecosoft Inc.).

All the data in this study were submitted to statistical analysis using the Kruskal–Wallace one way ANOVA by Ranks test for variables at the different MAC values within one vapour group and the Wilcoxon Ranks-sum test for two groups for the differences between paired values and between vapour groups at all MAC values, including the corrections appropriate for multiple comparisons.

RESULTS

The mean values of $\dot{V}\text{E}$, $V\text{T}$, $\bar{\dot{V}}\text{I}$, f, $T\text{E}$, $P\text{E}'_{\text{CO}_2}$, arterialized venous carbon dioxide and $F\text{I}_{\text{CO}_2}$, are shown in table V, and the mean values of $\dot{V}\text{E}$, $V\text{T}$, f, $P\text{E}'_{\text{CO}_2}$ and arterialized venous carbon dioxide tension are depicted in figures 2 and 3.

The significant results obtained in the study were as follows:

(1) While it was possible to measure the effects of halothane and isoflurane at three MAC values in nitrous oxide (1.25, 1.5, 1.75) and two MAC values in oxygen (1.0, 1.25) in two groups of eight children, this procedure proved to be impossible with enflurane. The degree of ventilatory depression produced by enflurane was so profound that, on ethical grounds, and because of doubts concerning the validity of the results obtained, this part of the study was abandoned after the first six subjects; in four children attempts to achieve

TABLE V. *Ventilatory effects of halothane, isoflurane and enflurane in three groups of unstimulated children. All values are mean (SD)*

	MAC with 65% nitrous oxide			MAC in oxygen	
	1.25	1.5	1.75	1.0	1.25
$\dot{V}\text{E}$ (ml kg^{-1} min^{-1})					
Halothane	142.1 (45.4)	122.7 (42.3)	106.02 (37.1)	107.2 (31.6)	98.04 (36.1)
Isoflurane	125.14 (18.9)	103.13 (23.8)	83.17 (21.05)	94.22 (21.53)	73.76 (26.1)
Enflurane	91.78 (6.8)	63.91 (10.6)	—	81.24 (15.7)	63.95 (7.3)
$V\text{T}$ (ml kg^{-1})					
Halothane	4.25 (1.0)	3.25 (0.9)	2.52 (0.7)	3.14 (0.67)	2.54 (0.65)
Isoflurane	4.13 (0.67)	2.91 (0.41)	2.21 (0.39)	3.26 (0.55)	2.28 (0.65)
Enflurane	3.72 (0.34)	2.60 (0.36)	—	3.25 (0.6)	2.41 (0.33)
$\bar{\dot{V}}\text{I}$ (ml kg^{-1} min^{-1})					
Halothane	362.5 (106.1)	311.8 (95.37)	268.5 (78.14)	284.52 (69.04)	262.37 (75.7)
Isoflurane	326.6 (50.3)	271.6 (52.1)	223.6 (48.03)	266.8 (48.2)	222.42 (61.9)
Enflurane	232.8 (34.8)	108.8 (21.8)	—	218.0 (33.1)	175.4 (16.7)
f (b.p.m.)					
Halothane	33.12 (6.05)	37.5 (6.8)	41.75 (7.12)	33.62 (4.86)	37.57 (5.77)
Isoflurane	30.62 (4.36)	35.37 (5.9)	37.75 (6.8)	29.08 (5.93)	32.41 (7.33)
Enflurane	24.66 (0.51)	24.5 (1.05)	—	25.0 (2.1)	26.8 (4.3)
$T\text{E}$ (s)					
Halothane	1.08 (0.22)	0.94 (0.18)	0.85 (0.16)	1.08 (0.22)	0.96 (0.18)
Isoflurane	1.19 (0.22)	1.04 (0.26)	1.00 (0.26)	1.35 (0.29)	1.24 (0.28)
Enflurane	1.35 (0.14)	1.50 (0.18)	—	1.49 (0.23)	1.18 (0.21)
$P\text{E}'_{\text{CO}_2}$ (kPa)					
Halothane	6.15 (0.6)	6.62 (0.71)	7.29 (0.88)	6.92 (0.87)	7.31 (0.98)
Isoflurane	6.13 (0.19)	6.65 (0 42)	7.66 (0.75)	7.43 (0.47)	7.66 (0.82)
Enflurane	7.32 (0.48)	8.55 (0.6)	—	8.13 (1.77)	8.96 (1.2)
Arterialized CO_2 tension (kPa)					
Halothane	5.62 (0.67)	6.14 (0.63)	6.74 (0.99)	6.78 (0.84)	7.10 (1.02)
Isoflurane	5.49 (0.16)	6.12 (0.46)	7.21 (0.62)	7.21 (0.72)	7.38 (1.06)
Enflurane	7.01 (0.41)	8.48 (0.44)	—	9.00 (0.87)	9.52 (0.46)
$F\text{I}_{\text{CO}_2}$ (kPa)					
Halothane	0.65 (0.51)	0.66 (0.56)	0.62 (0.36)	0.45 (0.22)	0.50 (0.21)
Isoflurane	0.46 (0.32)	0.42 (0.24)	0.44 (0.2)	0.18 (0.14)	0.43 (0.24)
Enflurane	0.04 (0.05)	0.04 (0.05)	—	0.07 (0.09)	0.13 (0.19)

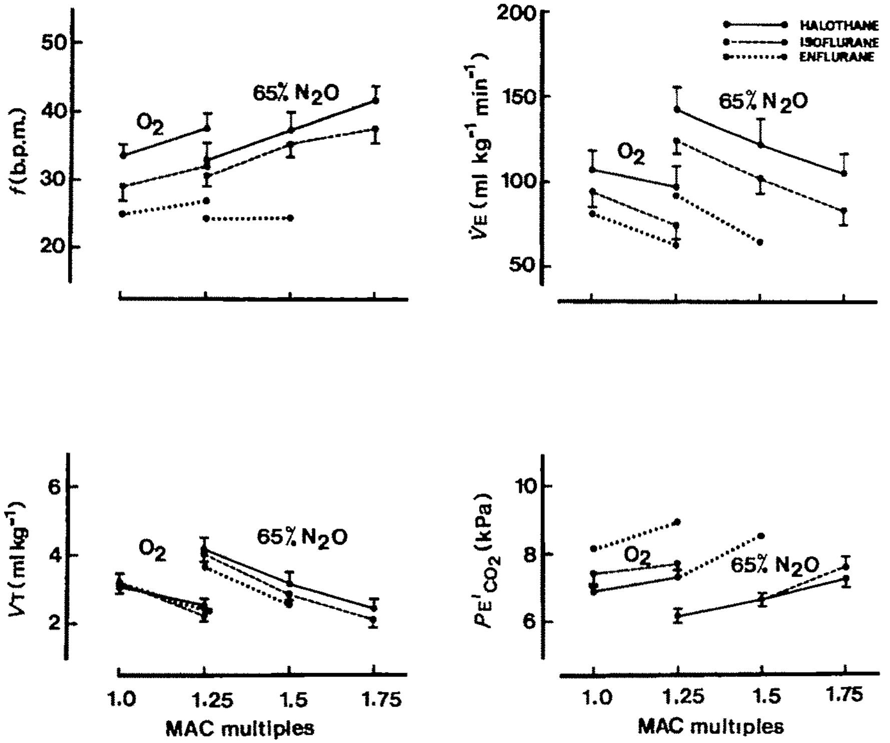

FIG. 2. Responses of ventilatory frequency (f), minute volume ($\dot{V}_E$), tidal volume (V_T) and end-tidal carbon dioxide tension ($P_{E'CO_2}$) in three groups of unstimulated children to halothane, isoflurane and enflurane at various MAC values in oxygen (left), and with 65% nitrous oxide (right). All values are mean (±SEM).

alveolar concentrations of 1.75 MAC enflurane with 65% nitrous oxide resulted in either apnoea or intermittent ventilation, as was also the case when attempts were made to achieve alveolar concentrations of 1.25 MAC in oxygen in two children. Consequently, the values recorded for MAC 1.75 enflurane in nitrous oxide have been omitted from table V and figures 2 and 3. Extreme difficulty was encountered in attempting to establish stable accurate alveolar concentrations of enflurane, despite repeated efforts with prolonged equilibration times. This problem is reflected in the alveolar concentrations depicted in table III and results from the combined effects of the profound depression of ventilation produced by low alveolar concentrations which were achieved rapidly as a result of the relative insolubility of the agent.

(2) As the values for $\dot{V}_E$, V_T and P_{CO_2} in table V and figures 2 and 3 reveal, the three agents produced depression of ventilation with significant hypercarbia at all values of MAC studied with the exception of halothane and isoflurane at MAC 1.25/nitrous oxide, where the tachypnoeic response was sufficient to prevent hypercarbia.

(3) The depression of ventilation produced by the three agents in combination with alveolar concentration of 65% nitrous oxide (in oxygen) increased in a dose-related fashion as their alveolar concentrations were increased; the relationships between the increasing carbon dioxide tension

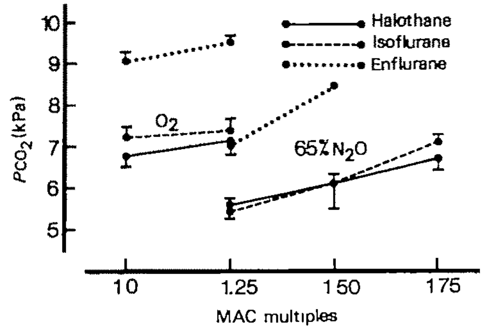

FIG. 3. Response of arterialized venous P_{CO_2} in three groups of unstimulated children to halothane, isoflurane and enflurane at various MAC values in oxygen (left) with 65% nitrous oxide (right). All values are mean (±SEM)

(end-tidal and arterialized venous) and increasing alveolar concentrations of the three agents was significant ($P < 0.05$), as were the decreases in V_T ($P < 0.01$), and $\dot{V}_I$ ($P < 0.05$) for halothane MAC 1.25–1.75/nitrous oxide and for isoflurane and enflurane MAC 1.25–1.5/nitrous oxide.

(4) Increasing alveolar concentrations of halothane were associated with an increase in ventilatory frequency which was statistically significant ($P < 0.05$). No increase in ventilatory frequency occurred in the enflurane group, and the increase in ventilatory frequency recorded in the isoflurane group did not achieve statistical significance. Increasing alveolar concentrations of halothane/nitrous oxide were also associated with a decrease in T_E, from 1.08 (0.22) s at MAC 1.25/nitrous oxide to 0.85 (0.16) s at MAC 1.75/nitrous oxide ($P < 0.05$), but no statistically significant changes in T_I/T^{tot} accompanied the increase in alveolar halothane concentrations.

(5) Comparison of the values recorded at MAC 1.25 in oxygen, with those recorded at MAC 1.25 with 65% nitrous oxide, revealed that the depression of ventilation produced by the three agents in oxygen was greater than that produced by equi-MAC concentrations in nitrous oxide: $P < 0.05$ for all variables in the halothane group, and for all variables except ventilation rate in the enflurane and isoflurane groups.

(6) Comparison of the effects of the three agents revealed that: (a) there was no statistical difference between the magnitude of the effects of halothane and isoflurane on mean $\dot{V}_E$, or carbon dioxide tension, but the tachypnoeic response to increasing halothane concentrations was significantly greater than that to isoflurane ($P < 0.05$). (b) There was no difference of any statistical significance in the degree of depression of V_T produced by the three agents at any MAC value studied in nitrous oxide or oxygen. (c) The values recorded for $\dot{V}_E$, and carbon dioxide tension in the enflurane group differed significantly ($P < 0.01$) from the values in the halothane and isoflurane groups. Enflurane produced markedly greater depression of $\dot{V}_E$ and increase in carbon dioxide tension than did either halothane or isoflurane.

DISCUSSION

The study was originally intended to establish the effects of three alveolar concentrations of each agent, MAC 1.0, 1.50 and 2.0 in oxygen, and the effects of alveolar mixtures of MAC 1.0, 1.50 and 2.0 with 65% nitrous oxide (in oxygen). However, it was considered unethical to proceed to the severe degrees of ventilatory depression produced by alveolar concentrations of 2.0 MAC, at which, in any event, episodes of apnoea would inevitably interfere with the validity of the results; nor could valid observations be made in the presence of the severe irregularity of ventilation in children attempting to breathe spontaneously through a tracheal tube at concentrations of 1.0 MAC in nitrous oxide. It was decided, therefore, that the effects of the agents should be studied in alveolar concentrations of 1.25, 1.5 and 1.75 MAC, but, again, early results indicated that severe degrees of hypoventilation were produced by concentrations in excess of 1.5 MAC in oxygen. For these reasons the final design of the study consisted of measuring the effects of three mixtures of each agent with nitrous oxide, 1.25, 1.5 and 1.75 MAC, and two concentrations in oxygen 1.0 and 1.25 MAC.

In considering the results, attention must be directed to the inspired carbon dioxide concentrations recorded, which indicate that some degree of rebreathing occurred in the halothane and isoflurane groups, with none in the enflurane group. As the minimal $\dot{V}_F/\dot{V}_E$ ratios recorded for the three agents, all at MAC 1.25/nitrous oxide, were 2.8 for halothane, 3.47 for isoflurane, and 4.92 for enflurane, the fresh gas flows used were obviously adequate. The rebreathing must, therefore, have resulted from the V_D (10 ml) of the apparatus, and the patterns of ventilation associated with the three agents. While the data on T_E in the enflurane group were insufficient to provide adequate statistical analysis, it is evident that the slow ventilatory rate and prolonged T_E associated with enflurane–nitrous oxide provided adequate time for the expired gases to reach the expiratory limb of the Bain system before inspiration commenced (Byrick and Janssen, 1980); this was not possible when a V_D of this size (which was essential to prevent turbulence at the flow head) was combined with the rapid ventilation rates and shortened expiratory times associated with halothane and isoflurane in children who have received no sedative pre-operative medication.

While strictly comparable studies, performed in unsedated children of the same age group before surgery commences, are not available, some evidence on the significance of the inspired carbon dioxide concentrations found can be derived from recent reports on halothane anaesthesia in children. Murat, Chaussain and Saint-Maurice (1985), in a study in smaller (20–68 months) unsedated children, recorded the same depression of V_T (3.34 (0.25) ml kg^{-1} at MAC 1.4 halothane/nitrous oxide) as this study, and showed that the addition of 2% inspired carbon dioxide, while producing significant increases in $\dot{V}_E$, V_T and $\dot{V}_I$, has no effect on ventilatory frequency. Lindahl, Charlton and Hatch (1985) in a study of ventilatory responses to rebreathing and carbon dioxide inhalation in smaller children (9.3–25 kg), showed that, while the carbon dioxide responsiveness, although diminished, was maintained during halothane/nitrous oxide anaesthesia in the range MAC 1.25–1.7, inspired carbon dioxide concentrations of the order of 1.45 (0.38)% produced no significant changes in end-tidal carbon dioxide concentration or ventilatory frequency. It is improbable, therefore, that the maximum mean $F_{I_{CO_2}}$ in the halothane (0.66%) or the isoflurane (0.46%) groups in this study contributed to the increases in $P_{E'_{CO_2}}$ and ventilatory rate recorded with these two agents.

Another study in small children (10–20 kg) (Murat et al., 1985) recorded an increase in ventilatory frequency associated with increasing concentrations of halothane/nitrous oxide and a decrease in T_I/T^{tot}, especially at high concentrations. Studies of the phrenic neurogram in vagotomized cats during IPPV (Nishino, Honda and Yonezawa, 1983) demonstrated that, if Pa_{CO_2} was increased while the halothane concentration remained constant, there was a progressive prolongation of T_E, with variable changes in T_I; increases in halothane concentrations with a constant Pa_{CO_2} produced a progressive shortening of T_E with virtually no change in T_I, and a consequent increase in ventilatory frequency. These studies revealed no consistent changes in T_I/T^{tot} in response to either increases in carbon dioxide tension or halothane concentration; while Nishino and colleagues concluded that the responses of T_E to carbon dioxide and halothane were consistent and opposite, they also demonstrated that, when the concentration of halothane *and* the carbon dioxide tension were increased, the T_E shortening effect of halothane was dominant.

These observations lead to the conclusion that the significant increase in respiratory frequency associated with increasing alveolar concentrations of halothane in this study, which was accompanied by a statistically significant reduction of T_E with no significant changes in T_I/T^{tot}, was the result of the increasing alveolar concentrations of halothane and not of the accompanying increases in carbon dioxide tension.

Nunn and Ezi-Ashi (1961) have shown that a resistance to breathing of 0.21 cm H_2O litre^{-1} min^{-1} could produce a reduction of 7% in ventilation, without affecting ventilatory frequency. Consequently, the resistance to gas flow produced by the equipment used in this study (table II) may have produced a fractional depression of $\dot{V}_E$ and V_T. However, since the resistances of the tracheal tubes used without the pneumotachograph were 0.1 cm H_2O litre^{-1} min^{-1} or less, it can be assumed that the true values of $\dot{V}_E$ and V_T in children breathing through a tracheal tube during anaesthesia are, at most, 2–3% greater than the values recorded in this study. Thus for example, the true V_T for the three agents at MAC 1.5/nitrous oxide would be approximately 0.1 ml greater than the values displayed in table V and figure 2.

Data directly comparable to the results described here (in that the studies were performed on unsedated patients not undergoing surgery, and arterial carbon dioxide tensions were also recorded) are to be found principally in the studies of the ventilatory effects of the volatile agents in adult volunteers, some of which also provided data on the effects of nitrous oxide (Hornbein et al., 1969; Eger et al., 1972; Lam et al., 1982). From these comparisons it is evident that the depression of ventilation produced in the children in this study, and the dose-related increase in ventilatory depression associated with increasing alveolar concentrations of the three agents, were substantially the same as those described in the adult.

The mean arterialized venous carbon dioxide tensions found in the children at alveolar concentrations of MAC 1.0 in oxygen of the three agents were not significantly different from those described in the adult: halothane 6.78 (0.84) kPa in the children, and 6.58 (0.33) in the adult (Hornbein et al., 1969); isoflurane 7.21 (0.72) kPa in the child and 6.93 (0.26) in the adult (Eger et al., 1972); enflurane 9.0 (0.87) kPa in the child and 8.6 (0.4) in the adult (Lam et al., 1982). If the MAC values used in the various studies are adjusted to one another, the increases in arterialized P_{CO_2} (fig. 3) closely resemble those described in the adult. The variable discrepancy between the end-tidal and arterialized venous carbon dioxide tensions recorded in this study is difficult to explain. While it may be tempting to attribute the fact that the arterialized venous values were less than the end-tidal partial pressures (in all recordings except enflurane MAC 1.0, 1.25 in oxygen) to the use of equilibration times which were adequate for the stabilization of end-tidal values, but not arterialized venous values, this argument would have to overcome a number of obstacles. In the first instance, the "reverse" gradient was established with all three agents at the first alveolar concentration measured (MAC 1.25/nitrous oxide), when the equilibration time had, in all patients, been at least 15 min; and the value recorded in the halothane group at that MAC (6.15 (0.6)kPa) was virtually identical with the value of 6.12 (0.23) recorded by Murat and coworkers (1985) with an MAC mixture of 1.31. Furthermore the second $P\text{E}'_{\text{CO}_2}$ value recorded, with halothane MAC 1.5/nitrous oxide (6.62 (0.71) kPa) does not differ significantly from the value of 6.89 (1.09) recorded at a MAC mixture of approximately 1.56 by Charlton, Lindahl and Hatch (1985) in another study of the effects of halothane on ventilation in children. In addition, the arterialized venous carbon dioxide tensions recorded in the children in this study differ very little from those recorded in the adults in the studies referred to above in which, without exception, extensive equilibration times were used. Unfortunately, arterial or arterialized venous carbon dioxide values were not recorded in the other studies on the effects of halothane on children referred to above. This problem, obviously, does not admit of an easy explanation, and further studies of the relationship of end-tidal and arterial values are in hand.

The decreases in tidal volume produced by the three agents at alveolar concentrations of MAC 1.0 in oxygen, which were virtually identical with one another, also resemble closely the values described in the adult: halothane 3.14 ml kg^{-1} in children and 3.62 ml kg^{-1} in adults (Hornbein et al., 1969); isoflurane 3.26 ml kg^{-1} in children and 3.16 ml kg^{-1} in adults (Eger et al., 1972); enflurane 3.25 ml kg^{-1} in children and 3.81 ml kg^{-1} in adults (Calverley et al., 1978). Again, increases in the alveolar concentrations of the three agents produced effects on tidal volumes very similar to those seen in the adult.

Furthermore, in the child as in the adult (Hornbein et al., 1969; Eger et al., 1972; Lam et al., 1982), the depression of ventilation produced by the three agents in oxygen was significantly greater than that produced by equi-MAC concentrations with nitrous oxide, as the values for $\dot{V}\text{E}$, $V\text{T}$ and $P\text{CO}_2$ recorded at MAC 1.25 reveal.

However, while the children responded to increases in the alveolar concentrations of halothane with a tachypnoea similar to that described in the adult (Munson et al., 1966), their responses to isoflurane and enflurane were the obverse of those described in the adult (Fourcade et al., 1971; Calverley et al., 1978); increasing alveolar concentrations of isoflurane were associated with a dose-related tachypnoea in the children, while there was no increase in rate of ventilation in response to increasing alveolar concentrations of enflurane.

The depression of ventilation produced by halothane and isoflurane in the children in this study, and their ventilatory responses to increasing alveolar concentrations of these two agents, were virtually identical. The only significant difference concerned the increases in ventilatory frequency which were recorded. However, while the increase in ventilatory frequency associated with increasing concentrations of halothane was statistically significant ($P < 0.05$), and the increase in frequency associated with isoflurane was not, it was, nonetheless, sufficient to maintain the end-tidal and arterialized venous $P\text{CO}_2$ tensions in the isoflurane group at values which did not differ significantly from those in the halothane group. Since all three agents produced equal depression of tidal volume at all MAC values, the profound depression of ventilation produced in the children by enflurane was clearly the result of the fact that no increase in ventilatory frequency was associated with its use.

From the data of these studies it would appear that the ventilatory effects of these three volatile agents in unstimulated children are similar to those described in the adult. There was no difference of any clinical importance between the magnitude of the depression of ventilation produced by halothane and isoflurane, and the clinical impression that isoflurane produces a greater degree of ventilatory depression than halothane, is almost certainly attributable to the rapid onset of the effects of isoflurane (Wren et al., 1985), which is conferred by its relative insolubility (Eger, 1981). The difficulties encountered in the use of enflurane, in children breathing spontaneously during anaesthesia, are the result of the profound depression of ventilation, and consequent fluctuations in the level of tissue saturation produced.

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CONGENITAL HEART MALFORMATIONS AND VENTILATORY EFFICIENCY IN CHILDREN

Effects of Lung Perfusion During Halothane Anaesthesia and Spontaneous Breathing

S. G. E. LINDAHL AND A.-K. OLSSON

SUMMARY

The efficiency of spontaneous ventilation during halothane anaesthesia was investigated in 18 infants and children with congenital heart disease presenting either with hyperperfusion and left-to-right shunt (group LR: $n = 10$, body weight 3.7–16 kg) or with hypoperfusion and right-to-left shunt (group RL: $n = 8$, body weight 3.4–12 kg). Minute ventilation ($\dot{V}E$) and tidal volume (V_T) were greater in group RL than in group LR ($P < 0.05$) while ventilatory rates were similar. Dynamic compliance and total pulmonary resistance were of the same magnitude in the two groups. Alveolar ventilation ($\dot{V}A$) calculated from arterial carbon dioxide tensions (Pa_{CO_2}) was the same in both groups while corresponding deadspace ventilation ($\dot{V}D$) was higher in group RL ($P < 0.01$). $\dot{V}E/\dot{V}CO_2$ and V_D/V_T ratios were higher in children with a diminished pulmonary blood flow than in children with an increased pulmonary blood flow ($P < 0.05$ and $P < 0.01$, respectively) indicating a less efficient gas exchange in children with a right-to-left shunt. This was compensated for by an increased inspiratory drive as reflected by higher V_T/T_I ratio ($P < 0.01$) and a more pronounced airway occlusion pressure ($P < 0.05$).

Lung compliance is decreased in awake, spontaneously breathing children with congenital heart disease who present with increased pulmonary blood flow (Wallgren, Geubelle and Koch, 1960; Howlett, 1972) whereas minute ventilation, alveolar ventilation and the arterial-to-end tidal carbon dioxide difference are similar to the values obtained in children who have a normal cardiopulmonary function (Lees, Way and Ross, 1967). The opposite is true in awake children whose heart disease results in a decrease in pulmonary blood flow (Lees et al., 1968; Howlett, 1972).

Anaesthesia alters the mechanics of the lung (Westbrook et al., 1973; Gilmour, Burnham and Craig, 1976; Hedenstierna and Santesson, 1979), and gives rise to mismatching of ventilation–perfusion (West, Dollery and Naimark, 1964) which impairs gas exchange and could, conceivably, worsen already compromised lung function in children with congenital cardiac malformations. Since such children often need repeated anaesthetics for open-heart surgery and various minor surgical and investigational procedures, investigation of their gas exchange, during anaesthesia and spontaneous ventilation, is of interest.

PATIENTS AND METHODS

Tidal volume ($V\text{T}$), ventilation rate (f), durations of inspiration ($T\text{I}$) and expiration ($T\text{E}$) and of the whole ventilatory cycle (T^{tot}), airway occlusion pressure ($P_{\text{aw}}{}^{0}$) and timing during occlusions (T^{0}), end-tidal carbon dioxide tension ($P\text{E}'_{\text{CO}_2}$), mixed expired carbon dioxide fraction ($F\bar{\text{E}}_{\text{CO}_2}$), arterial carbon dioxide tension (Pa_{CO_2}), and airway (P_{aw}) and oesophageal (P_{oe}) pressures were measured in 18 spontaneously breathing infants and children during halothane anaesthesia before cardiac surgery. Minute ventilation ($\dot{V}\text{E}$), carbon dioxide elimination ($\dot{V}\text{CO}_2$), alveolar ventilation ($\dot{V}\text{A}$), deadspace minute ventilation ($\dot{V}\text{D}$), $V\text{D}/V\text{T}$ and $\dot{V}\text{E}/\dot{V}\text{CO}_2$ ratios, dynamic compliance (C_{dyn})

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TABLE I. *Patient data, diagnosis and maintenance treatment. PDA = Patent ductus arteriosus; VSD = ventricular septal defect; APVD = anomalous pulmonary venous drainage; ASD = atrial septal defect; TGA = transposition of great arteries. Hb = Haemoglobin; Hct = haematocrit*

Patient no.	Age (yr/m/day)	Body weight (kg)	Hb (g litre^{1})	Hct (%)	Diagnosis	Maintenance treatment
Group LR						
1	1/2/19	10.9	116	37	PDA	—
2	1/4/27	9.6	132	39	VSD + Infundibular stenosis	Digitalis
3	4/11/17	14.4	137	40	APVD	—
4	0/1/29	3.7	138	37	Corrected transposition + VSD	Digitalis, diuretics
5	3/3/17	16.0	116	36	PDA	—
6	0/8/17	6.0	108	30	VSD	—
7	1/6/19	9.8	125	36	PDA	—
8	0/11/20	8.4	145	38	VSD + ASD, Mb Down	Digitalis
9	1/3/26	8.9	125	35	VSD	—
10	0/8/13	7.2	114	33	PDA	—
Group RL						
11	0/0/1	3.4	171	70	Pulmonary atresia, PDA	Prostaglandin
12	0/6/29	7.6	212	63	Pulmonary atresia, previous shunt	Digitalis, diuretics
13	2/9/0	12.0	201	64	TGA	—
14	0/5/0	5.9	135	43	Tetralogy of Fallot	Diuretic
15	0/2/8	4.2	201	62	Tricuspid atresia + pulmonary stenosis	—
16	0/7/4	6.9	190	56	Pulmonary atresia, previous shunt	—
17	1/5/3	9.8	220	65	Pulmonary atresia, previous shunt	—
18	0/2/4	4.2	168	68	VSD + tight pulmonary banding	Digitalis, diuretics

and total pulmonary resistance (TPR) were calculated.

Patients

All the children had congenital cardiac malformations and were scheduled for surgical correction of their anomaly(s). They were divided into two groups according to physical examination, chest x-ray, findings on cardiac catheterization, echocardiography, haemoglobin (Hb) concentration and haematocrit (Hct). There were 10 children with a normal Hb concentration, Hct below 40% and signs of a left-to-right shunt resulting in pulmonary hyperperfusion (group LR). Their body weights ranged from 3.7 to 16 kg, and their ages from 2 months to almost 5 yr. In the other group, in which there was right-to-left intracardiac shunting, all the children ($n = 8$) had a high Hb concentration, a Hct above 43% and showed signs of pulmonary hypoperfusion (group RL). These children weighed between 3.4 and 12 kg and were aged between 1 day and almost 3 yr. Further patient data are presented in table I. Parents gave their informed verbal consent to the study which was approved by the Hospital Ethics Committee.

Anaesthesia

The children were fasted for at least 4 h and those younger than 1 yr arrived in theatre unpremedicated. Older children were premedicated with a combination of diazepam 0.5 mg kg^{-1}, morphine 0.15 mg kg^{-1} and hyoscine 0.01 mg kg^{-1} given rectally 45–60 min before the induction of anaesthesia.

Anaesthesia was induced with nitrous oxide and halothane in oxygen ($F_{I_{O_2}}$ 0.5) via an anaesthetic face mask. In seven patients (one in group LR, six in group RL) thiopentone 2–3 mg kg^{-1} i.v. was given in addition. After induction a cannula was inserted to a peripheral vein and atropine 0.02 mg kg^{-1} and suxamethonium 1–1.5 mg kg^{-1}

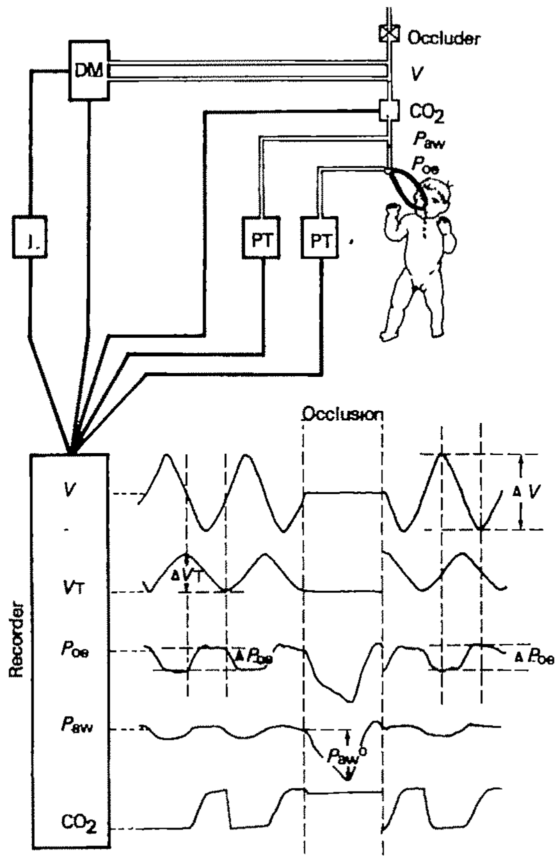

FIG. 1. Schematic presentation of recorded variables. The change in volume (ΔV_T) between points of zero flow was used for calculation of dynamic compliance and the flow ($\Delta\dot{V}$) between midvolume points was chosen for the calculation of total pulmonary resistance. Typical tracings for carbon dioxide concentration, airway (P_{aw}) and oesophageal (P_{oe}) pressures are shown. One occlusion test is illustrated.

were injected. Nasotracheal intubation was performed (cuffed tracheal tubes: Mallinkrodt). Once spontaneous ventilation had resumed, anaesthesia was maintained with nitrous oxide and 0.5–1% halothane in oxygen ($F_{I_{O_2}}$ 0.5). A Mapleson D system was used and fresh gas flows set high enough to avoid rebreathing. Radial artery and central venous cannulae were inserted.

Measuring apparatus

An in-line infra-red capnograph (Hewlett-Packard, 14360 A), a pneumotachograph (Fleisch No. 00 below 8 kg, Fleisch No. 0 above 8 kg) and connections for an airway occluder were placed in the apparatus deadspace. Airway pressures were measured at the tracheal tube connection (fig. 1). The deadspace of the system was 6 ml with the Fleisch No. 00 and 8 ml with Fleisch No. 0 (measured by water displacement). The inspiratory and expiratory resistances of the measuring apparatus were 1.6 kPa litre^{-1} s^{-1} for Fleisch No. 00 and 1.8 kPa litre^{-1} s^{-1} for Fleisch No. 0 at a flow rate of 8 litre min^{-1}. No measurements were made until the halothane concentration and the level of anaesthesia were considered to be stable and at least 25 min had elapsed since induction. The investigation delayed the start of surgery by approximately 15–20 min during which time, however, the bladder catheter and the venous cannulae were inserted, and routine clinical monitoring established. All measurements were performed before surgery during spontaneous ventilation—which is the normal practice for these patients at our institution until venous access has been secured and the trachea intubated.

$\dot{V}_E$ was measured by electrical integration of the flow signal from the heated pneumotachograph and a differential pressure manometer (Validyne, MP 45-1-871, range ± 2 cm H_2O). The Fleisch No. 00 was linear for flow rates up to 8 litre min^{-1} and Fleisch No. 0 up to flow rates of 16 litre min^{-1}. The capnograph response time to a complete deflection was 0.05 s and a well identified end-tidal plateau was observed in all patients. P_{aw} and P_{oe} were measured by Druck pressure transducers (PDCR-75). For the measurements of oesophageal pressures fluid-filled catheters were used (Olsson and Lindahl, 1985). Flow, volume, pressures and $P_{E'_{CO_2}}$ were recorded on an ink-jet recorder (Siemens-Elema, EM 81). Flow and volume were calibrated with an accurate pump, the capnograph with a known carbon dioxide tension (corrections for nitrous oxide being made) and the pressure transducers at −2 kPa.

Expired gas passed to a dry gas meter (Standard gas meter, AB Nordgas, Stockholm, Sweden) and then to a three-way valve from which a timed collection (over 5 min) of a measured volume of gas could be made into a Douglas bag. The mean exhaled fraction of carbon dioxide ($F_{E_{CO_2}}$) in the bag was then immediately measured by the capnograph. Arterial blood (0.5 ml) was sampled in heparinized syringes and analysed within 3 min (Radiometer, Copenhagen, Denmark). The blood-gas machine was calibrated daily.

After the collection of the gas and measurements of the indices of ventilation, occlusion tests during two to three breaths were performed. The airway occluder was controlled electrically by the

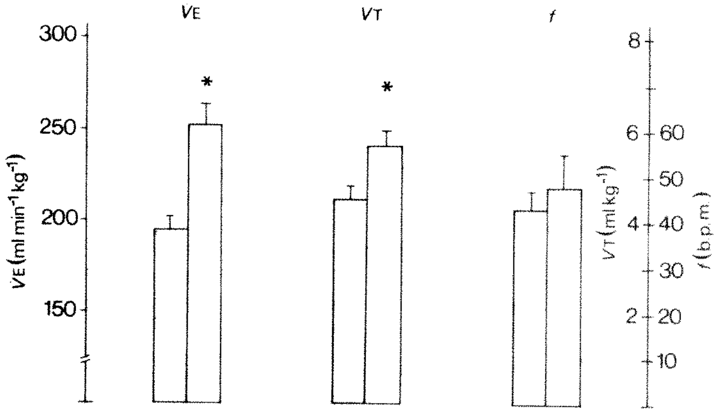

FIG. 2. Mean values (±SEM) of minute ventilation ($\dot{V}$E), tidal volume (VT) and ventilatory rate (f) in the group of children with overperfused lungs (LR: shaded bars), and in the group with oligaemic lungs (RL: open bars). $^{**}P < 0.05$ for the differences between groups LR and RL.

pneumotachograph so that occlusions occurred precisely when expiration switched to inspiration, that is at the functional residual capacity (FRC). The response time of the occluder was 0.03 s.

Calculations

$\dot{V}$E, $\dot{V}$A, VT, $\dot{V}$D, and $\dot{V}CO_2$ are presented at body temperature and pressure saturated (BTPS). The following formulae were used:

$$\dot{V}CO_2(\text{ml min}^{-1}) = \text{gas collection } \dot{V}\text{E} \times F\bar{\text{E}}CO_2$$

$$\dot{V}\text{A}\,(\text{ml min}^{-1}) = \frac{\dot{V}CO_2 \times P_B}{Pa_{CO_2}};$$

$$\dot{V}\text{A}^{\text{Bohr}}\,(\text{ml min}^{-1}) = \frac{\dot{V}CO_2 \times P_B}{P\text{E}'_{CO_2}}$$

$$\dot{V}\text{D} = \dot{V}\text{E} - \dot{V}\text{A};\ \dot{V}\text{D}^{\text{Bohr}} = \dot{V}\text{E} - \dot{V}\text{A}^{\text{Bohr}}$$

$$C_{\text{dyn}}(\text{ml kPa}^{-1}) = \frac{V\text{T}}{P\text{E} - P\text{I}}$$

$$\text{TPR (kPa litre}^{-1}\text{ s}^{-1}) = \frac{P\text{E} - P\text{I}}{\dot{V}}$$

where PE and PI are the mean of eight transpulmonary pressures calculated during zero flow after inspiration (PI) and expiration (PE) for calculations of C_{dyn}, and at mid-volume points during inspiration and expiration for calculations of total pulmonary resistance (TPR) (see also figure 1). P_B is atmospheric pressure in kPa. To use transpulmonary pressures for the calculation of C_{dyn} and TPR a ratio of 0.9:1.1 between oesophageal ($P_{oe}{}^0$) and airway pressure ($P_{aw}{}^0$) during airway occlusions was required. This was achieved in nine patients in group LR and in five patients in group RL. At occlusion the decreases in airway pressure during 0.1 s ($\Delta P/\Delta t$) of the fast and of the slow phases were also calculated.

Statistics

Mean values, standard deviation (SD) and standard error of the mean (SEM) were calculated. Mean values and SEM are presented. Paired and unpaired two-sided t tests were carried out. Probability values less than 0.05 were considered to indicate statistical significance.

RESULTS

Arterial pressures (mean arterial pressure (MAP): 64±4 mm Hg group LR; 57±5 mm Hg group RL), heart rates (143±5 beat min^{-1} group LR; 139±6 beat min^{-1} group RL) and halothane concentrations (0.73±0.06% group LR; 0.81±0.08% group RL) were similar in the two groups during the measurements of ventilation and gas exchange.

Pulmonary ventilation

Minute ventilation was 35% greater in children with oligaemic lungs (256±22 ml min^{-1} kg^{-1}) compared with those who had overperfused lungs (189±14 ml min^{-1} kg^{-1}) ($P < 0.05$) (fig. 2). Rates of ventilation were similar in the two groups (fig. 2) and so were the $T\text{I}/T^{\text{tot}}$ ratios (0.44±0.01 in group LR and 0.43±0.01 in group RL). VT was 4.5±0.3 ml kg^{-1} in group LR and 5.7±0.3 ml kg^{-1} in group RL ($P < 0.05$) (fig. 2). Pa_{CO_2} was lower

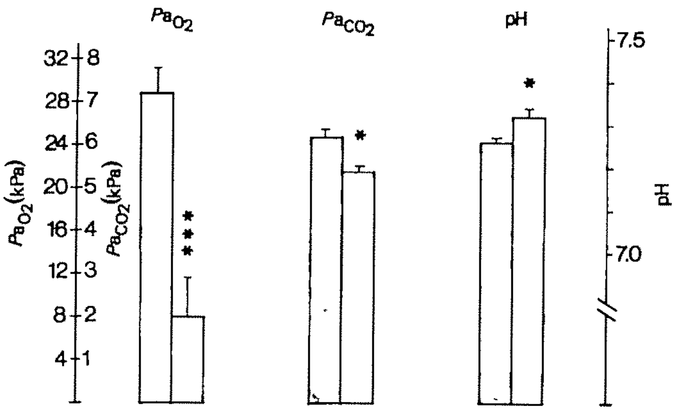

FIG. 3. Mean values (±SEM) of arterial oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}) tensions and of pH in groups LR (shaded bars) and RL (open bars). $^*P < 0.05$; $^{***}P < 0.001$ for the differences between the two groups.

TABLE II. *Mean values* (±*SEM*) *of dynamic compliance* (C_{dyn}) (n = *9 in group LR and* n = *5 in group RL*) *and total pulmonary resistance* (*TPR*) (n = *9 in group LR and* n = *5 in group RL*)

	Left to right shunts (group LR)	Right to left shunts (group RL)
C_{dyn} (ml kPa^{-1} kg^{-1})	10.4±0.8	8.1±1.5
TPR (kPa $litre^{-1}$ s^{-1})	3.9±0.6	5.8±1.4

(5.4±0.1 kPa) in group RL than in group LR (6.2±0.3 kPa) ($P < 0.05$) (fig. 3). Base excess was similar in the two groups, while pH was greater in the children with pulmonary hypoperfusion (7.32±0.02 *v.* 7.26±0.01; $P < 0.05$). The Pa_{O_2} values in the cyanotic group (RL) were lower than in the acyanotic group (LR) ($P < 0.001$) (fig. 3). The lowest Pa_{O_2} measured in group RL was 5.4 kPa while no subnormal values were found in the other group. C_{dyn} and TPR were similar in the two groups (table II).

Gas exchange

Mean carbon dioxide elimination ($\dot{V}CO_2$) was slightly but not significantly lower in children with hypoperfused lungs. $\dot{V}A$ was similar in the two groups (fig. 4, table IV). Physiological deadspace ventilation ($\dot{V}D$) (ml min^{-1} kg^{-1}) was 91% greater in group RL (145±21 ml min^{-1} kg^{-1}) than in

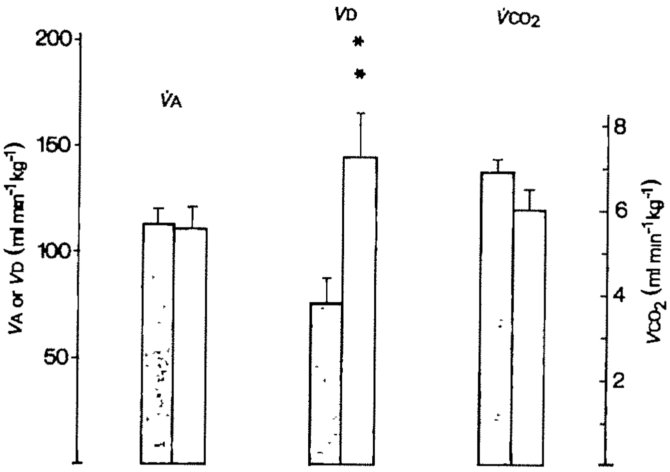

FIG. 4. Mean values (±SEM) of alveolar ventilation ($\dot{V}A$), deadspace ventilation ($\dot{V}D$) and carbon dioxide elimination ($\dot{V}CO_2$) in groups LR (shaded bars) and RL (open bars). $^{**}P < 0.01$ for the difference between the two groups.

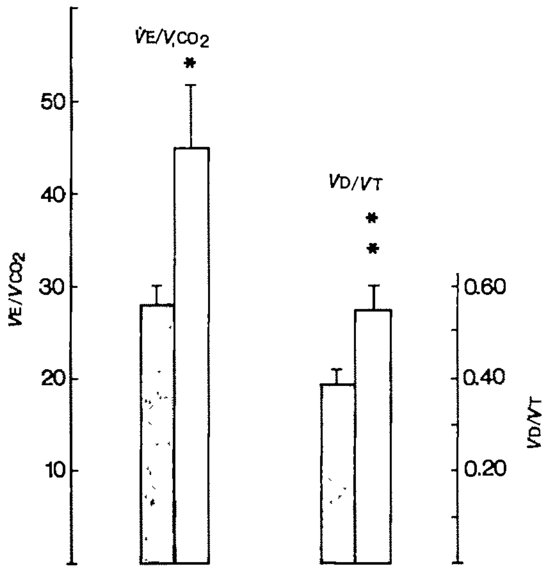

FIG. 5. Mean values (±SEM) of $\dot{V}$E/$\dot{V}$CO$_2$ and VD/VT ratios in groups LR (shaded bars) and RL (open bars). *$P < 0.05$; **$P < 0.01$ for differences between the two groups.

group LR (76±12 ml min^{-1} kg^{-1}) ($P < 0.01$) (fig. 4). VD/VT was 0.39±0.03 in group LR and 0.55±0.05 in group RL ($P < 0.01$) (fig. 5) and corresponding values for $\dot{V}$E/$\dot{V}$CO$_2$ ratio were 28±2 and 45±7, respectively ($P < 0.05$) (fig. 5).

There was no difference between arterial (6.2±0.3 kPa) and end-tidal (6.2±0.2 kPa) carbon dioxide tensions in children with hyperperfused lungs, while those with hypoperfused lungs had a Pa_{CO_2} of 5.4±0.1 kPa and a PE$'_{CO_2}$ of 4.5±0.2 kPa—a difference of 0.9 kPa ($P < 0.01$). In group LR alveolar ventilation ($\dot{V}$A$^{\text{Bohr}}$) and VD$^{\text{Bohr}}$/VT ratio were similar to $\dot{V}$A and VD/VT—that is, values calculated from Pa_{CO_2} (fig. 6). In group RL, however, the deviations between $\dot{V}$A$^{\text{Bohr}}$ and $\dot{V}$A ($P < 0.01$) as well as between VD$^{\text{Bohr}}$/VT and VD/VT ($P < 0.01$) were greater and individual relations between these variables are presented in figure 6.

Ventilatory drive

The mean inspiratory flow (VT/TI) (ml kg^{-1} s^{-1}) was less in group LR (7.1±0.4 ml kg^{-1} s^{-1}) than in group RL (9.8±0.7 ml kg^{-1} s^{-1}) ($P < 0.01$). Airway occlusion pressure curves were biphasic, with an initial fast phase followed by a slower one. $P_{aw}{}^{o}{}_{fast}$ was more pronounced in children with oligaemic than in those with overperfused lungs ($P < 0.05$) (fig. 7). The duration of the fast phase was similar in the two groups (table III). The maximal occluded airway pressure ($P_{aw}{}^{o}{}_{max}$) was more pronounced in group RL than in group LR ($P < 0.05$) (fig. 7) and the duration from the start of the occluded breath to the maximal occluded intra-airway pressure ($T^{o}{}_{max}$) was longer in group RL than in group LR ($P < 0.05$) (fig. 7) (table III). The $\Delta P/\Delta t$ ratio of the initial fast phase was

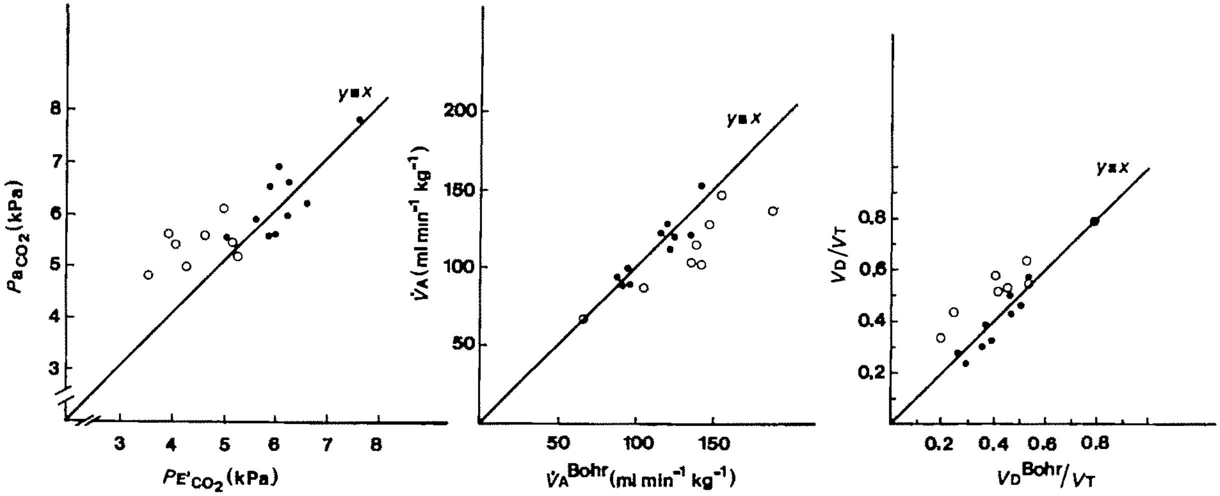

FIG. 6. Relations in each individual between Pa_{CO_2} and PE$'_{CO_2}$, $\dot{V}$A and $\dot{V}$A$^{\text{Bohr}}$ as well as VD/VT and VD$^{\text{Bohr}}$/VT. Filled circles are values from children with overperfused lungs and open circles from children with oligaemic lungs. Lines of identity are drawn in each diagram.

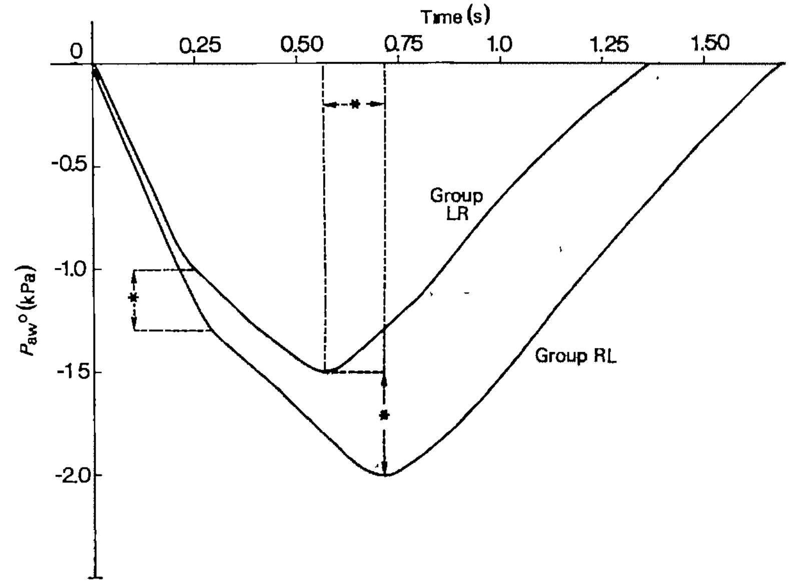

FIG. 7. Airway occlusion pressure curves in the two groups drawn schematically from mean values of pressure and time. The pressure differences of $P_{aw}{}^{o}{}_{fast}$ and of $P_{aw}{}^{o}{}_{max}$ between the two groups are indicated as well as the differences in time to reach $P_{aw}{}^{o}{}_{max}$ in the two groups. $*P < 0.05$ for the differences between the groups.

TABLE III. *Mean values (±SEM) of airway occlusion pressures after the initial fast phase* ($P_{aw}{}^{o}{}_{fast}$) *and the maximal occluded pressure* ($P_{aw}{}^{o}{}_{max}$) *and of corresponding times* ($T^{o}{}_{fast}$ *and* $T^{o}{}_{max}$) *as well as the duration of an occluded breath* ($T^{o\,tot}$) *and the* $T^{o}{}_{max}/T^{o\,tot}$ *ratio* $*P < 0.05$ *for the difference between groups LR and RL*

	$P_{aw}{}^{o}{}_{fast}$ (kPa)	$P_{aw}{}^{o}{}_{max}$ (kPa)	$T^{o}{}_{fast}$ (s)	$T^{o}{}_{max}$ (s)	$T^{o\,tot}$ (s)	$T^{o}{}_{max}/T^{o\,tot}$
Group LR	1.0±0.1	1.5±0.1	0.24±0 02	0.56±0.04	1.38±0.09	0.40±0.01
	*	*		*		
Group RL	1.3±0.1	2.0±0.2	0.29±0.03	0.71±0.05	1.68±0.17	0.43±0.02

5.2±0.6 kPa s^{-1} in group LR and 6.2±0.7 kPa s^{-1} in group RL (ns) and of the slower phase 2.2±0.3 kPa s^{-1} and 3.6±0.6 kPa s^{-1} ($P < 0.05$), respectively (fig. 7). The $T^{o}{}_{max}/T^{o\,tot}$ ratio was similar in the two groups (table III). In group LR the $T^{o}{}_{max}/T^{o\,tot}$ ratio was lower than the T_{I}/T^{tot} ratio at unoccluded breathing ($P < 0.01$) which, however, was not the case in group RL.

DISCUSSION

In this study, no measurements were performed until at least 25 min had elapsed after the induction of anaesthesia. Recently, Gallagher and Black (1985) showed that after 30 min the alveolar-to-inspired halothane ratio was greater than 0.7 in children with normal cardiopulmonary function. This was most probably also the case in the present study for children with over-perfused lungs, while a somewhat lower ratio might exist in children with hypoperfused lungs. Insertion of bladder catheters, venous cannulae and other preparatory preoperative non-surgical procedures were not thought to have any influence on the actual measurements obtained.

In the group of children with increased pulmonary blood flow as a result of a left-to-right shunt, cardiac failure was treated in three, but none had any signs of cardiac decompensation before anaesthesia and surgery. In those with a diminished pulmonary blood flow, patients number 11 and 18 (table I) had the smallest ($Pa_{CO_2}-PE'_{CO_2}$) (fig. 6). Patient No. 11, who was investigated during his first day of life, was deeply

TABLE IV. *Mean values ($\pm 1SD$) of $\dot{V}_E$, V_T and $\dot{V}_A$ from this study compared with those of spontaneously breathing healthy children anaesthetized with halothane* (*Olsson and Lindahl, 1986*) *and of awake children* (*Lees, Way and Ross, 1967; Lees et al., 1968*). §*Values for $\dot{V}_A$ calculated from end-tidal carbon dioxide tensions* ($\dot{V}_A^{Bohr}$). *$*P < 0.05$ for the differences between group LR and RL; †$P < 0.05$ for the difference between data from Olsson and Lindahl (1986) and group LR in this study; ‡‡‡$P < 0.001$ for the difference between data from Olsson and Lindahl (1986) and group RL in this study*

	Anaesthetized			Awake		
	This study		Olsson and Lindahl (1986)	Lees, Way and Ross (1967)	Lees, Way and Ross (1967)	Lees et al. (1968)
	Group LR	Group RL	Normal lung perfusion	Normal lung perfusion	Hyper-perfusion	Hypo-perfusion
$\dot{V}_E$ (ml min^{-1} kg^{-1})	189±45*	256±61	228±28†	198±28	217±26	265±71
V_T (ml kg^{-1})	4.5±0.8*	5.7±1.0	4.1±0.7‡‡‡	7.3±0.8	6.0±1.3	8.7±1.8
$\dot{V}_A$ (ml min^{-1} kg^{-1})	113±21	111±27	115±25§	135±19§	150±18§	207±61§

cyanotic as a result of pulmonary atresia and needed a continuous prostaglandin infusion to keep the ductus arteriosus open during preparation for surgery (Freed et al., 1981). Although his Pa_{O_2} was low and Hct was 70% (high, even at this early age) and he was cyanotic, ($Pa_{CO_2} - PE'_{CO_2}$) was only -0.04 kPa. This was unexpected and might be explained by the prostaglandin infusion which has a vasodilatory effect on pulmonary arteries (Lewis et al., 1981) and could have improved the ventilation–perfusion relationship. The other child in group RL (No. 18) with a small ($Pa_{CO_2} - PE'_{CO_2}$) had previously required a subclavian flap because of a preductal coarctation of the aorta, and pulmonary banding had been performed because of a large ventricular septal defect. About 1 month after the first operation, signs of pulmonary hypoperfusion developed and by the time debanding was performed, the patient was being treated for cardiac failure and was thought to have a slow pulmonary circulation. Since pulmonary congestion increases pulmonary blood volume, more blood comes to the alveoli, increasing the alveolar carbon dioxide tension and this may have contributed to the small ($Pa_{CO_2} - PE'_{CO_2}$) in this patient, in spite of low lung perfusion.

Children with oligaemic lungs had larger tidal volumes than children with overperfused lungs, while ventilatory rates were similar. Tidal volumes in group RL were also greater ($P < 0.001$) than in children with normal cardiopulmonary function (Olsson and Lindahl, 1986) (table IV). Anaesthetized children with normal and increased lung perfusion have similar tidal volumes as awake children (Lees, Way and Ross, 1967; table IV). Furthermore, the significantly greater tidal volumes found in group RL, compared with group LR, agree with the findings of Lees and colleagues (1968) in awake patients (table IV).

To achieve adequate alveolar ventilation, the children with oligaemic lungs required larger minute ventilations compared with those who had overperfused lungs ($P < 0.05$). Since $\dot{V}_A$ was similar in the two groups, there must have been a much larger proportion of wasted ventilation in group RL (fig. 4)—that is, greater V_D/V_T ratios ($P < 0.01$) (fig. 5). However, this seems to be contrary to the results obtained by Lees and colleagues (1968). They found that $\dot{V}_E$ (mean ± 1SD) was 217 ± 26 ml min^{-1} kg^{-1} in awake children with hyperperfused lungs and 265 ± 71 ml min^{-1} kg^{-1} in children with hypoperfused lungs, that is 22% greater. Simultaneously, they found that the corresponding value of alveolar ventilation was 38% greater (table IV). Therefore, in awake children ventilation seemed to be more efficient in children with oligaemic lungs. However, the alveolar ventilation calculated by Lees and colleagues was based on end-tidal carbon dioxide tensions ($\dot{V}_A^{Bohr}$) and, since their patients with hypoperfusion had a large ($Pa_{CO_2} - PE'_{CO_2}$) it

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was an over estimate. Assuming that in patients with oligaemic lungs $\dot{V}_A^{Bohr}$ exceeded $\dot{V}_A$ by 22% as was the case in the present study, their value of 207 ml min^{-1} kg^{-1} becomes 170 ml min^{-1} kg^{-1}, and brings their data into conformity with the findings in the present study.

Children with diminished pulmonary blood flow require an enhanced ventilatory drive to maintain carbon dioxide homeostasis. Since ventilatory rates and T_I/T^{tot} ratios were similar in the two groups the increase in V_T/T_I ratio in group RL was attributable to larger tidal volumes, indicating increased ventilatory motor activity. This was also supported by the greater airway occlusion pressures in group RL. During occlusion, the airway pressures in both the fast and slow phases were more negative in group LR. This indicates that both the neuronal output of the intended breath from the ventilatory motor centre, shown by the early phase (Cherniack et al., 1976), and the total number of nerve impulses to the ventilatory muscles, reflected by the slower phase and maximal occlusion pressure (Kay, 1979; Lindahl and Olsson, 1986), were increased.

It is concluded that adequate gas exchange was achieved during the short period of time (up to 45 min) that elapsed in this study. In children with cardiac anomalies which resulted in an increase in pulmonary blood flow gas exchange was efficient; tidal volumes were similar to those obtained in the normal child. Invasive and non-invasive calculations of gas exchange were similar. In children with diminished pulmonary blood flow, however, ventilation was inefficient with high $\dot{V}_E/\dot{V}_{CO_2}$ and V_D/V_T ratios and increases in ventilatory drive. In these, invasive and non-invasive calculations of gas exchange differed greatly because of the large value of ($Pa_{CO_2} - PE'_{CO_2}$).

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ANAESTHESIA FOR PAEDIATRIC TONSILLECTOMY

Comparison of Spontaneous Ventilation and Intermittent Positive Pressure Ventilation

P. J. STOW AND J. B. WHITE

SUMMARY

Fifty children undergoing tonsillectomy were anaesthetized using either a spontaneous ventilation (SV) technique with halothane (and nitrous oxide in oxygen) or intermittent positive pressure ventilation (IPPV) (with nitrous oxide, in oxygen) facilitated by atracurium 0.5 mg kg^{-1}*. Time to full recovery was significantly less in the IPPV group (1.8±3.79 min) than the SV group (20.0±6.77 min) (*$P < 0.001$*) and ventilated children had a better quality of long-term recovery (sleep score 1.02 for the SV and 1.44 for the IPPV groups) (*$P < 0.01$*). Apart from a significantly greater* E'_{CO_2} *in the halothane group (7.3 kPa±0.9 compared with 5.1 kPa±0.5) (*$P < 0.001$*), there was no significant difference in operative or postoperative morbidity.*

Tonsillectomy in children requires an anaesthetic technique which allows rapid and smooth recovery of protective airway reflexes at the end of surgery. The majority of anaesthetists follow the recommendations of Doughty (1957a) and use a technique incorporating spontaneous ventilation and an inhalation agent. However, when used for ENT surgery in children, such a technique has been shown to be associated with unacceptable hypercarbia (Valentin, Lomholt and Thorup, 1982), arrhythmias (Lindgren, 1981a; Sigurdsson and Lindahl, 1983) and prolonged recovery (Lindgren, 1981b). The improved efficiency of artificial ventilation, particularly in infants, has been said to justify its frequent use during paediatric anaesthesia (Hulse, Lindahl and Hatch, 1984).

The present study was designed to compare, in children undergoing tonsillectomy, spontaneous ventilation (SV) and intermittent positive pressure ventilation (IPPV) with regard to intra-operative complications, quality and duration of recovery and postoperative morbidity.

PATIENTS AND METHODS

Patients

The study was approved by the local Ethics Committee. Fifty children were studied and all fulfilled the following criteria: ASA group I or II, age 3–12 yr and undergoing tonsillectomy either as a separate procedure or in combination with adenoidectomy or myringotomy, or both. All children were seen by one of the authors the day before surgery—which took place in the morning. Premedication was pethidine 1 mg kg^{-1} and atropine 20 μg kg^{-1} i.m. 1 h before operation. On arrival in the anaesthetic room each child was randomly allocated to receive either SV (group A) or an IPPV technique (group B).

Anaesthetic technique

Each child was anaesthetized by one of the authors. Induction was with thiopentone 4 mg kg^{-1} and in group A the trachea was intubated after the administration of suxamethonium 1.5 mg kg^{-1}. Ventilation was assisted until the return of normal neuromuscular function, after which 1–3% halothane and 66% nitrous oxide in oxygen were breathed spontaneously. In children weighing less than 20 kg, the Jackson–Rees modification of Ayre's T-piece was used with a fresh gas flow of 15 × ventilatory frequency × body weight (kg) ml min^{-1} (Hulse, Lindahl and Hatch, 1984). In children heavier than 20 kg a Bain system was used with a fresh gas flow of 150 ml kg^{-1}.

Children in group B received atracurium

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TABLE I. *A simplified anaesthetic recovery score* (*Steward, 1975*)

	Points
Consciousness:	
Awake	2
Responding to stimuli	1
Not responding	0
Airway:	
Coughing on command or crying	2
Maintaining good airway	1
Airway requires maintenance	0
Movement:	
Moving limbs purposefully	2
Non-purposefully	1
Not moving	0
TOTAL	

TABLE II. *Patient characteristics*

	Group A	Group B
No. of patients (M/F)	15/10	15/10
Average age (yr)	6.41	7.85
(range)	(3.3–11.8)	(4.2–11.5)
Average weight (kg)	23.9	24.7
(range)	(14.7–43.0)	(16.4–52.5)

TABLE III. *Surgical procedure*

	Group A	Group B
Tonsillectomy (T)	8	6
Adenotonsillectomy (T&A)	11	15
Myringotomy, T&A	5	3
Oesophagoscopy, T&A	0	1
Myringotomy, T&A and antral washout	1	0
Duration of anaesthesia (min)	30.8	29.4
(range)	(22–48)	(20–47)

0.5 mg kg^{-1} and after 2 min of controlled ventilation by face mask the trachea was intubated. Throughout anaesthesia the lungs were ventilated by hand with 66% nitrous oxide in oxygen using the Jackson–Rees modification of Ayre's T-piece with a fresh gas flow of $0.8 \times \sqrt{\text{body weight (kg)}}$ litre min^{-1} (Nightingale, 1982). Supplements of atracurium 0.1 mg kg^{-1} were given when necessary and after the completion of surgery, residual neuromuscular blockade was antagonized with neostigmine 50 $\mu\text{g kg}^{-1}$ (plus atropine 20 $\mu\text{g kg}^{-1}$).

All children had the tracheal tube removed while in the left lateral position with slight head-down tilt.

Monitoring

Electrocardiogram (Roche 105) leads were attached to each child after transfer to the operating table. End-tidal carbon dioxide tension was monitored throughout anaesthesia using a calibrated capnograph (Gould Mark II) with the sensor placed adjacent to the tracheal tube.

The time of extubation was noted and the child transferred to a recovery ward where recovery was assessed by one of the authors, blind to the anaesthetic technique used. Children were ascribed a score of 0–6 at 5-min intervals according to the recovery scoring system described by Steward (1975) (table I).

The time taken to achieve a score of 6 was recorded, as was the time from extubation to opening eyes on command. Overall quality of recovery was assessed as "good", a child that recovered happily and with minimum distress; "satisfactory", a child that was settled during most of its stay in the recovery ward; or "poor", a child that was distressed or tearful throughout the majority of its recovery period.

Patients were then returned to the children's ward where trained nursing staff graded their recovery with respect to sleep, distress and pain with a score of 0, 1 or 2. Episodes of vomiting were also recorded. Each child was assessed for a period of 6 h.

Student's *t* test was used for the parametric data, and the Chi square and Mann–Whitney tests were used to assess statistical significance of the non-parametric data.

RESULTS

The two groups were similar in terms of weight and duration of anaesthesia (table II). The type of surgery performed is shown in table III. Mean inspired halothane concentration for the period of anaesthesia in group A is shown in table IV.

There was no significant difference between groups A and B in peroperative heart rate, but the maximum end-tidal carbon dioxide concentration was significantly greater in group A ($P < 0.001$) (table V). No arryhthmias were seen in group A and only two short episodes of a sinus arryhthmia in group B. Operating conditions were satisfactory in both groups and there were no surgical complications.

At extubation a cough reflex was present in a significantly greater number of children in group B ($P < 0.001$). The mean time to achieve a score

TABLE IV. *Mean inspired halothane concentration (group A) (assuming MAC halothane = 0.75%)*

Mean "MAC minutes" of halothane	79.8
Mean duration of anaesthesia	29.4
Mean MAC halothane per minute of anaesthesia	2.54

TABLE V. *Per-operative measurements.** P < *0.001*

	Group A	Group B
Heart rate (beat min^{-1})	138.4	139.2
(SD)	(15.8)	(20.0)
End-tidal CO_2 (kPa)	7.27	5.13*
(SD)	(0.87)	(0.52)
Arrhythmias		
Nil	25	23
Sinus arrhythmia	0	2
At extubation:		
Coughing	1	16
Laryngospasm	0	0
No response	24	9

TABLE VI. *Observations on the recovery ward. EOC = Eye opening on command.* *P < *0.001*

	Group A	Group B
Time to score 6	20.0 *	1.8
Mean (SD) (min)	(6.77)	(3.79)
Time to EOC	22.5 *	2.6
Mean (SD) (min)	(9.86)	(3.53)
Bleeding	3	0
Laryngospasm	1	0
Quality of recovery:		
Good	12	11
Satisfactory	9	4
Poor	4	10
Analgesia one dose	4	3
Retching	0	6
Vomiting	3	2

TABLE VII. *Observations on the children's ward.* *P < *0.01*

	Group A	Group B
Sleep score		
a.m. 0	3	0
1	13	10
2	9	15
p.m. 0	8	3
1	14	11
2	3	11
Mean sleep score	1.02	1.44*
Distress score		
a.m. 0	6	10
1	15	14
2	4	1
p.m. 0	11	11
1	9	11
2	5	3
Mean distress score	0.84	0.66
Analgesia		
Two doses	1	0
One dose	1	3
Nil	23	22

TABLE VIII. *Incidence of vomiting. (*A number of children vomited in more than one category—for example early and late)*

		Group A	Group B
In recovery	Nil	22	23
	1/2	3	2
Early (6–9 h)	Nil	18	16
	1/2	4	8
	3+	3	1
Late (> 9 h)	Nil	19	17
	1/2	5	6
	3+	1	2
Overall percentage of children vomiting*			
	Mild	44%	68%
	Serious	16%	12%

of 6 and the mean time to opening eyes on command were significantly shorter in group B ($P < 0.001$) (table VI).

The quality of recovery was judged as good in 48% and 44% of children in groups A and B, respectively, but 40% of children in group B were considered to have a poor recovery, compared with 16% in group A. However, there was no statistically significant difference between the two groups in terms of the quality of recovery.

The analgesic requirements in each group were similar, but there was a higher incidence of retching in the immediate recovery period in the ventilated children. The incidence of vomiting was similar in both groups (table VI). There was only one brief episode of laryngospasm in a child from group A, and three episodes of minor bleeding, which settled without intervention.

Observation of longer-term recovery showed that children who had been ventilated were less distressed and more likely to sleep for longer periods than those who received halothane (table VII). The differences in sleep score were significant ($P < 0.01$).

The overall incidence of vomiting (during the first 24 h after anaesthesia) was 44% in group A and 68% in group B, the incidence of serious vomiting (three or more episodes) being similar in each group (table VIII). There was no significant

TABLE IX. *Surgical complications*

	Group A	Group B
Discharged at 48 h	23	22
Discharge delayed	2	3
Reason for delayed discharge	Clot in fossa Congested fossae and pyrexia	Clots in fossa (three patients)

difference in the incidence of surgical complications (table IX).

DISCUSSION

In otolaryngological surgery, particularly in children, rapid recovery of airway reflexes is essential: the upper airway is compromised by the presence of blood and secretions, and oedema of the oropharynx and increased laryngeal irritability may predispose to laryngospasm. Lindgren (1981b) compared halothane and enflurane anaesthesia using controlled or "assisted" ventilation in 132 children and found the mean time from extubation to opening eyes on command to be 29 min in the halothane group and 21 min in the enflurane group. These figures compare favourably with our mean value of 22.5 min in the SV group. Where there is a risk of bleeding in the oropharynx it is the time to control of the airway that is more important and the significance of time from extubation to opening eyes on command is perhaps debatable. By using a scoring system, such as Steward's, it is possible to compare this with the time to achieve airway control and, in our study, the mean time to achieve the latter in the halothane (spontaneous breathing) group was 18 min compared with 2.6 min in the ventilated group; 18 min still represents a prolonged recovery time.

There can be little doubt that IPPV results in rapid awakening in children, but there have been few studies to show that this is advantageous. In this unit it is the policy of the ENT surgeons to retain all children in the recovery room for a period of 1 h following tonsillectomy. Although not significantly different, the authors feel that children who received an IPPV technique, and who awoke rapidly, were more likely to be distressed by this period because of maternal separation. However, other factors must be considered and a child that has been anaesthetized using an IPPV technique may well be distressed by waking rapidly on a cold trolley and with a stomach containing quantities of gas. A child who has received halothane, on the other hand, may awaken more slowly and, with episodes of shivering, will be warm and, perhaps, more settled. Children in the IPPV group tended to be more settled on the ward and to sleep for significantly longer periods than children who received halothane. This finding suggests that the former children are content and more likely to sleep, which could be considered a natural reaction following surgery and anaesthesia, whilst children having received halothane remain irritable and restless for longer periods.

After the introduction of Doughty's modification of the Boyle–Davis gag in the late 1950's (Doughty, 1957b), tracheal intubation has justifiably become routine in anaesthetic practice for paediatric adenotonsillectomy. Doughty advocated spontaneous ventilation with nitrous oxide and oxygen plus a volatile agent and commented that "halothane... enabled a very light level of narcosis without coughing on the tube" and a very rapid recovery of consciousness. This is the technique which has probably been the most commonly used over the past 25 yr. In the only definitive study of ventilation during such a technique for tonsillectomy in children, Valentin, Lomholt and Thorup (1982) demonstrated a median maximum end-tidal carbon dioxide concentration of 7% with 41% of children having a value of greater than 7%. In their study they used the Bain system, but were unable to decrease the end-tidal carbon dioxide concentration by increasing the fresh gas flow or by changing to a non-rebreathing circuit, and recommended the use of assisted or controlled ventilation for tonsillectomy. The mean end-tidal carbon dioxide concentration of 7.3% in the children anaesthetized with halothane in our study was similar, and is a value which many anaesthetists would consider unacceptable. The high deadspace ventilation during spontaneous ventilation in small children undergoing general surgical procedures and its subsequent reduction by IPPV justifies the frequent use of controlled ventilation during anaesthesia in this age group (Hulse, Lindahl and Harch, 1984).

Two criticisms are often levelled against the use of IPPV and non-depolarizing myoneural blocking drugs for ENT surgery in children: first, the relatively prolonged duration of action of the neuromuscular blockers, and the need for antagonism with neostigmine (Hannington-Kiff, 1985); second, the risk of accidental disconnection during IPPV. Atracurium, which allows a mean time of recovery of 95% of twitch height of 29.0 min in children (Brandom, Cook and Rudd, 1983), would seem to have the ideal duration of action for this type of surgery and we have encountered no problems that could be attributed to its use. Although disconnection of the circuit from the tracheal tube remains a possibility, the use of manual ventilation minimizes the likelihood of this passing unnoticed.

The absence of arrhythmias in the halothane group in our study is perhaps surprising. Sigurdsson and Lindahl (1983) showed that the incidence of cardiac arrhythmia in children breathing spontaneously during halothane anaesthesia for adenoidectomy was as high as 72% compared with 32% during enflurane anaesthesia. In 20% of patients the arrhythmia was ventricular. Lindgren (1981a) demonstrated junctional rhythm in up to 33% of children undergoing tonsillectomy and adenoidectomy during halothane or enflurane anaesthesia. However, the mean heart rate in each group in our study was high, and this may be a reflection of increased catecholamine concentrations as a result of either hypercarbia or a light plane of anaesthesia. Sigurdsson, Lindahl and Norden (1984) measured catecholamine concentrations during adenoidectomy under halothane or enflurane anaesthesia and found that they were unchanged during enflurane anaesthesia, but were significantly higher during undisturbed halothane anaesthesia and increased by up to 300% during surgery. They postulated that the difference may be caused by a stimulating effect of halothane on the release of endogenous catecholamines. This observation correlates well with a high incidence of ventricular arrhythmia and one contributory factor may be hypercarbia. The highest mean $P\text{E}'_{\text{CO}_2}$ in that study was 8.0 kPa.

In the present study the overall incidence of vomiting was greater in the ventilated group but, according to the criteria of Smith and Manford (1974), there was no difference in the incidence of "serious" vomiting. The greater incidence in ventilated children may, in part, be the result of the entry of nitrous oxide to the stomach at induction, and this is reflected in the number of children in this group who retched soon after reaching the recovery room. Passage of an orogastric tube and aspiration of gas from the stomach soon after intubation may have reduced the likelihood of this occurrence.

In conclusion, we feel that the use of IPPV for tonsillectomy in children is rational, and allows a significantly more rapid return of protective reflexes. However, rapid awakening may be associated with greater distress during initial recovery, which may be related to maternal separation, but seems to be followed by better long-term recovery. There was no difference in anaesthetic and surgical morbidity between the two groups.

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COMPARISON OF TEMAZEPAM ELIXIR AND TRIMEPRAZINE SYRUP AS ORAL PREMEDICATION IN CHILDREN UNDERGOING TONSILLECTOMY AND ASSOCIATED PROCEDURES

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SUMMARY

Temazepam 0.5, 1.0 and 1.5 mg kg^{-1} in an elixir formulation (Euhypnos Elixir), was compared with trimeprazine tartrate 3 mg kg^{-1} in a syrup (Vallergan Forte Syrup), as premedication in 220 children (ASA grade I) undergoing tonsillectomy and associated procedures. Each patient was randomly allocated to one of the four treatments. The administration was blind to the observers in theatre, recovery room and postoperative ward, who assessed each patient according to a total of 14 criteria. A modelling technique allowed account to be taken of the effects of concomitant variables (e.g. age and duration of anaesthesia) where appropriate. No statistically significant difference was found between the efficacy of the treatments. The only statistically significant differences were that temazepam was associated with more ectopic beats under anaesthesia ($P = 0.03$ or 0.002, depending on the test applied), more postoperative vomiting ($P = 0.04$) and more postoperative restlessness ($P < 0.0001$).

Although some anaesthetists believe that the presence of the mother is the most effective "premedication" for young children, the design of modern operating theatres makes this difficult. However, the premedication of children for elective inpatient surgery is an accepted anaesthetic practice (Doughty, 1957, 1962; Binning et al., 1962; Davies and Doughty, 1966; Haq and Dundee, 1968) and it is worthwhile seeking improvements in that practice—particularly since the variety of premedicant agents used by anaesthetists indicates that no one agent has a general advantage over another. The main advantage of the oral route of administration over the i.m. is that the child accepts a drink of a coloured, flavoured syrup more readily than an injection (Doughty, 1959); the main disadvantage is the possible variable timing, and the adequacy of the therapeutic effect as a result of the variable absorption of the drug from the gastrointestinal tract.

The trend of premedication away from basal narcosis to one of anxiolysis and sedation has led to the use of benzodiazepines such as diazepam, lorazepam and, more recently, temazepam (Norris, 1969; Dundee and Haslett, 1970; Galloon, Gale and Lancee, 1977; Amarasekara, 1980; Douglas et al., 1980; Beechey, Eltringham and Studd, 1981; Bradshaw, 1981). Phenothiazines have long been used in children (Binning et al., 1962; Davies and Doughty, 1966; Haq and Dundee, 1968) although, recently, benzodiazepines have also been investigated (Lindgren, Saarnivaara and Himberg, 1980; Furness, Boyle and Fee, 1986; Padfield, Twohig and Fraser, 1986).

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The phenothiazine, trimeprazine tartrate, has been used widely as an oral premedication and investigated extensively. It has many merits: effective sedation, antisialagogue activity and an antiemetic effect. However, it may cause undue postoperative pallor (Davies and Doughty, 1966) and some adverse cardiac responses have been reported in young children (Loan and Cuthbert, 1985).

Temazepam, a relatively new, short-acting 1,4 benzodiazepine, has been used for premedication in adults, with satisfactory results (Amarasekara, 1980; Beechey, Eltringham and Studd, 1981) and has recently become available in an elixir formulation (10 mg in 5 ml, Euhypnos Elixir, Farmitalia Carlo Erba Ltd). A study was undertaken to compare the use of temazepam in this form, with trimeprazine tartrate in a syrup (Vallergan Forte Syrup) as premedication in children. The trial was based on the assumption that trimeprazine is an acceptable premedicant in children which, despite some disadvantages, is widely, although by no means universally, used. The study was not designed to establish whether trimeprazine or temazepam is an effective premedicant but only whether, in an appropriate dose, temazepam is "better" (or at least no worse) than a standard dose of trimeprazine.

The two drugs are an example of the situation where the new drug is believed to produce, in a dose-related manner, many of the effects of the established drug, and there is an accepted "standard" dose of the established drug, at least in local practice, which is thought to produce an optimum compromise between wanted and unwanted effects. In these circumstances, it is desirable to determine, for each relevant response, the dose of the new drug which is equipotent with the standard dose of the established drug. If the new drug has a lower equipotent dose for the desirable than for the undesirable responses, it is to be preferred; if the reverse is true the established drug is preferable.

If the magnitude of a particular response is insensitive to dose, or if the response is very variable between patients, then the confidence limits of the estimated equipotent dose for that response may be too wide to be of any value. The best that can be done then is to determine whether the magnitude of that response is significantly greater for one drug than for the other *at the doses used in the trial.*

In local practice the dose of trimeprazine is invariably 3 mg kg^{-1}, so this was adopted as the standard dose of the established drug. Therefore, the study was designed to try to determine, for all responses of interest, the dose of temazepam which was equipotent with trimeprazine 3 mg kg^{-1}. Temazepam had not previously been used in children, so a preliminary clinical assessment was undertaken. On the basis of the results, three doses (0.5, 1.0 and 1.5 mg kg^{-1}) were chosen as being likely to include the equipotent dose for most responses. Therefore, a randomized, observer-blind trial was planned, using these doses, in children undergoing tonsillectomy and associated procedures. The study received the approval of the hospital ethics committee.

PATIENTS AND METHODS

General

Two hundred and twenty children were entered to the trial and randomly allocated to receive trimeprazine tartrate 3 mg kg^{-1} or temazepam 0.5, 1.0 or 1.5 mg kg^{-1}. The only requirements for inclusion in the trial were that written informed consent had been obtained from the parents and that, at the preoperative assessment performed by Dr David L. Thomas (DLT), the child was judged to be in the ASA grade I category of fitness. Parents were not present at induction.

When a child entered the trial, a sealed, numbered envelope containing the treatment code defining the premedication to be used for that child was attached to the patient's notes. The following day, a qualified nurse on the preoperative ward opened the envelope and administered the specified premedication, without any antisialagogue, approximately 90 min before the anticipated start of surgery. Since temazepam elixir is green and trimeprazine is red the treatment was, to that extent, not blind to the patient nor to the administering nurse. However, no traces of the colour difference were visible at the time of the intubation, so that the observations made by the anaesthetist (DLT) were blind. Anaesthesia was induced with sodium thiopentone 5 mg kg^{-1} (and suxamethonium chloride 1 mg kg^{-1}) i.v., through a standard 23-gauge Butterfly needle. Anaesthesia was maintained with the child breathing spontaneously through a tracheal tube connected to a Bain coaxial breathing system supplied with 1–2 % halothane in a flow of nitrous

TABLE I. *Responses observed, with ranges of scores used or of measurements recorded*

- Preoperative on the ward
  - Problems following premedication: 0/1
    (None/one or more)
- Preoperative in theatre
  - Salivation on arrival in theatre: 0/1
    (Satisfactory/unsatisfactory)
  - Demeanour on arrival in theatre: 0–5
    (Noisy/tearful/apprehensive/serious/cheerful/sleepy)
  - Response to venepuncture: 0–4
    (Abandoned/crying started/audible response/winced/no response)
  - Hand withdrawal thereafter: 0/1
    (Unsatisfactory/satisfactory)
  - Preoperative ventilatory frequency: 12–60 b.p.m.
- Peroperative
  - Mean peroperative spontaneous ventilatory frequency: 17–65 b.p.m.
  - Problems under anaesthesia: 0–2
    (None/unifocal ectopic beats/multifocal ectopics)
- Postoperative
  - Duration of stay in recovery room: 4–45 min
  - Requirement for a postoperative analgesic: 0/1
    (nil/some)
  - Retching: 0–6
  - Vomiting: 0–6
  - Restlessness: 0–6
  - Pallor: 0–6
    (All the above four scores indicate the number of 30-min periods, within the first 3 h on the ward, in which the observation was true except that, in the case of vomiting, the score was increased by 1 if vomiting was recorded in the recovery room—but the maximum score achieved was then still only 3.)

TABLE II. *Explanatory variables observed, with ranges of values*

- Drug and dose
  - Trimeprazine tartrate: 3 mg kg^{-1}
  - Temazepam: 0.5, 1.0, 1.5 mg kg^{-1}
- Patient
  - Age: 2 years 9 months–14 years 5 months
  - Body weight: 13–49 kg
  - Sex: M/F
- Times
  - From premedication to arrival in theatre: 60–160 min
  - From premedication to arrival in recovery room: 82–188 min
  - From premedication to arrival in recovery ward: 100–200 min
  - Duration of anaesthesia: 12–44 min
- Other
  - Number of operations additional to tonsillectomy: 0–4
  - Code for grade of surgeon: 0–3
    (SHO/registrar/senior registrar/consultant)
  - Code for identity of surgeon: 0–7
  - Code for identity of nurse making recovery-ward observations: 0–10

oxide 6 litre min^{-1} plus oxygen 3 litre min^{-1}. At the end of the operation the child was transferred to the recovery room and from there, when the nurse deemed recovery to be adequate, to a recovery ward different from that in which the premedication was administered. Thus the nurses who made observations in the recovery ward were unaware of the treatment given.

The responses observed are listed in table I, but a few details need explanation. "Problems following premedication" were assorted free-format comments by the nurse on the preoperative ward and were the only observations that were not observer-blind. The scales used for assessing demeanour, response to venepuncture, and hand withdrawal thereafter were those of Doughty (1959). Peroperative ventilatory frequency was expressed as the mean of measurements made at 5-min intervals from the time that spontaneous breathing returned following induction until leaving the theatre. Ectopic beats (a "problem under anaesthesia") were detected from the ECG which was used as a monitor throughout the operation. (Arterial pressure and heart rate were measured before and at 5-min intervals during the operation, but the results were never a cause of clinical concern, except in relation to the ectopic beats, and were not processed.) When ectopic beats occurred, manual ventilation was instigated until the arrhythmia ceased. No pharmacological therapy was administered.

Variables which were observed in the expectation that they might explain some of the variation in the responses are listed in table II. Those listed under "Other" were included on the basis that the number of additional operations and the skill of the surgeon might influence the amount of postoperative pain and, hence, restlessness in the postoperative ward. The 11 nurses making the observations on that ward were separately identified on the basis that, for example, what one nurse recorded as "restless" might be recorded by another as "not restless". The additional operations comprised almost every combination and permutation of adenoidectomy, uni- and bi-lateral myringotomy, bi-lateral antral washout, and "other". It was not considered worth treating them as separate explanatory variables.

Statistical

For the analysis of the results a modelling technique was developed, based on the statistical computer-package "GLIM" (Generalised Linear

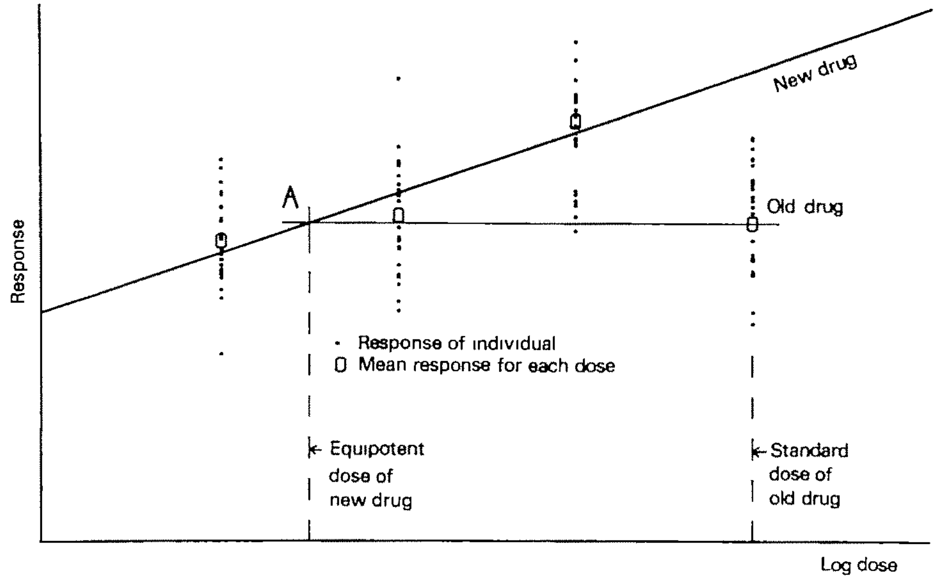

FIG. 1. Hypothetical dependence of a continuously variable, Normally distributed, response on log dose. Three doses of a new drug and one "standard" dose of an old drug have been used. The horizontal line is at the level of the mean response to the standard dose of the old drug. Its intersection A, with the straight line fitted to the response to the new drug, indicates the dose of the new drug which is equipotent with the standard dose of the old drug.

Interactive Modelling) (Baker and Nelder, 1978) and the "bootstrap" technique of Efron (Diaconis and Efron, 1983). This is described in detail elsewhere (Mapleson, 1986), but is outlined here for completeness.

The basis of the method is illustrated in figure 1 for hypothetical data corresponding to the general structure of the present study (three doses of the new drug, one of the old): the response of each patient has been plotted against log dose; a straight line has been fitted to the results for the new drug; and the point A on this line, at which the predicted response to the new drug is the same as the mean response to the standard dose of the old drug, indicates the equipotent dose of the new drug for the type of response in question.

This basic approach has been extended in four ways: to give valid results when the deviations of the responses from the fitted line are not Normally distributed, but can be shown to conform to one of the other distributions available in GLIM; to allow, where appropriate, for the effects of additional explanatory variables from table II by combining them into a single predictor of the response; to allow, where appropriate, for a sigmoid relationship between the response and this predictor; and to provide estimates of the 95% confidence limits of the equipotent dose. The method also allows the inclusion of "interactions" between explanatory variables; for example, the rate of dependence of a response on the time since premedication being different for the two drugs. The criteria for the inclusion of an additional explanatory variable, or an interaction, were that it was thought likely to affect the response in question, that its effect was significant ($P < 0.05$), and that its effect was plausible in direction and magnitude (see Appendix).

The technique can be applied, not only to responses measured on a continuous scale, but also to responses recorded as discrete data: quantal data (e.g. satisfactory/unsatisfactory) or, with some restrictions, counts of events or ordinal data.

For those responses which yielded very wide confidence limits (upper limit more than 10 times the lower limit), recourse was had to a straight comparison of the responses to the two drugs, pooling the results for all three doses of temazepam. The modelling technique was used here if it showed, for a given response, that the difference between the mean magnitudes of response to the two drugs was contributed to significantly by one or more of the variables in table II. For other responses, appropriate conventional two-group tests were used.

RESULTS

Of the 220 patients entered to the trial, 16 were withdrawn for reasons unconnected with the premedication: "operation cancelled" (four), "procedure not followed" (seven) or "returned to theatre because of excessive bleeding" (five). This left 204 patients for the response "problems following premedication". In three, the problem was that the child refused the premedication completely. These three patients were, therefore, excluded from the trial except in respect of this one response. The other problems, sometimes more than one per child, included "restless" (six instances), "confused" (four), "fell out of bed" (four) and coughing/hiccuping (three). Any such problem or combination of problems was allocated a score of 1, as opposed to 0 when no problem was reported. This left 201 patients for all the other responses, 54 of whom received trimeprazine 3 mg kg^{-1}, and 47, 50 and 50 of whom received temazepam 0.5, 1.0 and 1.5 mg kg^{-1}, respectively.

Of the responses in table I, salivation was always "satisfactory" and the requirement for a postoperative analgesic was always "nil". The other 12 responses were analysed by the modelling technique (Mapleson, 1986), in order to obtain an estimate of the dose of temazepam which was equipotent with trimeprazine tartrate 3 mg kg^{-1}. In only three instances was the dependence of response on dose sufficiently significant ($P < 0.01$) to lead to 95% confidence limits of the equipotent dose that were close enough to be of any value (table III). Even then, the limits included all three doses of temazepam.

For the other nine responses, dependence of response on dose did not reach even the 5% level of significance, so they were assessed either by the modified modelling technique, if that was appropriate (see above), or by conventional two-group tests. The resulting probabilities are listed in table IV, together with the direction of the difference (where it approached or reached significance) and the statistical test used. It is also worth recording that, although most of the "problems following premedication" were associated with temazepam and not trimeprazine, the difference between the two drugs was less significant for each of the individual problems than the non-significant result given in table IV for all problems taken together.

TABLE III. *Effect of increasing dose, and estimate and 95% confidence limits of the dose of temazepam which is equipotent with trimeprazine tartrate 3 mg* kg^{-1}, *for those responses in which the limits were not excessively wide*

Response	Effect of increasing dose	Equipotent dose (mg kg^{-1}) Estimate	95% Limits
Peroperative ventilatory frequency	Faster frequency	1.2	0.7–3.0
Duration in recovery room	Longer duration	0.9	0.3–2.4
Postoperative pallor	Greater incidence	1.0	0.5–1.7

DISCUSSION

It is disappointing that only three responses yielded equipotent doses with usable confidence limits, and even these are hardly close (table III). This is despite using a sophisticated modelling technique, capable of allowing for the effects of all the explanatory variables in table II. In fact only age and duration of anaesthesia ever met the criteria for inclusion in the model and none of the interactions did so. However, it is interesting that the identity of the nurse did approach significance in explaining the variation in postoperative restlessness.

Sedatives usually depress ventilation. Therefore, it is at first sight surprising that increasing the dose of temazepam *increased* the ventilatory frequency (table III). However, as with trichloroethylene, this may well be associated with a decrease in alveolar ventilation. This seems likely since, when ectopic beats occurred, presumably as a result of increased carbon dioxide tension in the presence of halothane, they were relieved by manual ventilation.

The wideness of the confidence limits of equipotent dose arises mainly from the non-significance of the dependence of most responses on dose. A number of features may have combined to prevent real dependencies of response on dose showing significantly: the limited range of doses, the wide range of responses to any given dose, and the inclusion of only 200 patients. However, the response "problems following premedication"

TABLE IV. *Direction and significance of the differences in responses to temazepam and trimeprazine at the doses used. †Given only when the difference approaches or reaches significance. ‡Probability that difference as large as or larger than that observed can be attributed to chance. §Problems* v. *no problems. *Incorporating allowance for effect of age* (*Mapleson, 1986*)

Response	Temazepam compared with trimeprazine†	*P*‡	Test used
Problems following premedication	More problems	0.12	Fisher-exact
Demeanour	—	0.75	Model*
Response to venepuncture	—	0.79	Model*
Hand withdrawal	—	0.24	Fisher-exact
Preoperative ventilatory frequency	Faster frequency	0.05	Model*
Problems under anaesthesia	More problems	0.03	Mann–Whitney
(ectopic beats)		0.002	Fisher-exact§
Postoperative retching	—	0.31	Mann–Whitney
Postoperative vomiting	More vomiting	0.04	Mann–Whitney
Postoperative restlessness	More restlessness	< 0.0001	Mann–Whitney

may have been genuinely independent of dose: the green colour of the temazepam preparation may have been less attractive to the children than the red of the trimeprazine and may have had a psychological effect on behaviour before the operation. Alternatively, the nurses, who knew that the usual colour of the premedication was red, might have been biased to notice more problems with the green solution—may, indeed, have thought it their duty to draw attention to them as part of the "experiment".

A primary aim in premedicating children is to ensure that the child is in a satisfactory state on arrival in theatre. The three responses which reflect this, demeanour, response to venepuncture, and hand withdrawal, all showed non-significant differences between the two drugs. This indicates that, in these respects, any of the three doses of temazepam (0.5, 1.0 or 1.5 mg kg^{-1}) chosen on the basis of the preliminary clinical assessment, may be equipotent with 3 mg kg^{-1} of trimeprazine. This is broadly supported by the fact that Furness, Boyle and Lee (1986), comparing the effects of trimeprazine 3 mg kg^{-1} with temazepam 1 mg kg^{-1}, found no significant difference in efficacy or apprehension. Also, Padfield, Twohig and Fraser (1986), comparing a larger dose of trimeprazine (4 mg kg^{-1}) with temazepam 1 mg kg^{-1}, found a better "attitude" (approximately equivalent to our "demeanour") with trimeprazine ($P = 0.025$) but a non-significant difference in "behaviour" (approximately equivalent to our "response to venepuncture"). Therefore, the estimated equipotent dose for pallor (1.0 mg kg^{-1}, with confidence limits of 0.5–1.7 mg kg^{-1}) (table III) does not provide any support for the hope that there would be less postoperative pallor with temazepam. On the other hand, at the doses given, temazepam was associated with significantly more problems under anaesthesia (ventricular ectopic beats) ($P = 0.03$ or 0.002 depending on the test applied (table IV)), more postoperative vomiting ($P = 0.04$) and more postoperative restlessness ($P < 0.0001$). Furness, Boyle and Lee (1986) found no cardiac arrhythmias with either temazepam or trimeprazine, but this was probably a result of the substitution of isoflurane for halothane for maintenance of anaesthesia. Padfield, Twohig and Fraser (1986) also found more postoperative vomiting with temazepam than with trimeprazine.

CONCLUSION

In this study, the only significant differences between the two drugs seem to favour trimeprazine rather than temazepam, although the wide confidence limits may conceal some differences in favour of temazepam.

APPENDIX

CHOICE OF ADDITIONAL EXPLANATORY VARIABLES

In both methods of using the model, the criteria for including an additional explanatory variable were: (1) that the variable should have been selected as a candidate for inclusion before commencing the analysis; (2) that the effect should be significant ($P < 0.05$ was used in this study); and (3) that the effect should be plausible in direction and magnitude. In most instances in the present trial, if an additional explanatory variable had a significant effect on a response, the effect was clearly plausible; a greater age led to a more restrained demeanour, to a more controlled response to venepuncture, and to lesser pre- and peroperative ventilatory frequencies; a greater duration of anaesthesia led to more problems during anaesthesia and to a longer stay in the recovery room.

In one instance the predicted change was not obviously plausible: the peroperative ventilatory frequency was greater for a greater duration of anaesthesia ($t = 3.36$, d.f. = 196) or for a greater number of operations additional to tonsillectomy ($t = 3.12$, d.f. = 196); when both were included in the model (along with drug, log dose and age) both were of only borderline significance ($t = 2.26$ and 1.91, respectively; d.f. = 195). However, the tonsillectomy was always performed first and anaesthesia was then lightened for any subsequent, less painful operations. Therefore, the greater the number of additional operations the longer the duration of anaesthesia, the lighter the mean depth of anaesthesia and, arguably, the greater the mean peroperative ventilatory frequency. Since the dependence on duration of anaesthesia was the more significant, this variable was retained and the other rejected.

In the remaining instance the plausibility of the predicted change was equivocal. The demeanour on arrival in the anaesthetic room showed a highly significant dependence on the time since the premedication was administered, provided that separate gradients against time were allowed for the two drugs. Qualitatively, this could be explained on a pharmacokinetic basis: in adults, the time of peak plasma concentration of temazepam is about 1 h (Pickup, Rogers and Launchbury, 1984) (the shortest time from premedication to arrival in theatre) while, for trimeprazine, it is about 3 h (Johnson and Masters, 1962) (more than the longest time). Quantitatively, however, the explanation fails: in the model, when the two drugs are allowed separate dependencies of demeanour on time, the implication is that a 20-min change from the mean time of 99 min since premedication produced a 10-fold change in the calculated potency ratio; whereas, when the results of Pickup, Rogers and Lauchbury and those of Johnson and Masters were plotted on a common graph, this showed only a 1.2-fold change in concentration ratio in the same circumstances. Therefore, time was rejected as an explanatory variable. This does not imply that demeanour is independent of time since premedication, only that the predicted difference in time dependence, between the two drugs, is much too large to be plausible.

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PROPOFOL OR THIOPENTONE: EFFECTS ON INTRAOCULAR PRESSURE ASSOCIATED WITH INDUCTION OF ANAESTHESIA AND TRACHEAL INTUBATION (FACILITATED WITH SUXAMETHONIUM)

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Propofol (2.6 diisopropylphenol), a non-barbiturate anaesthetic agent in an emulsion formulation, provides a smooth induction of anaesthesia without major adverse effect, and is associated with rapid clear-headed recovery (Cummings et al., 1984; Nightingale et al., 1984; Kay and Healy, 1985; MacKenzie and Grant, 1985). A previous study in non-intubated patients showed that the administration of propofol was associated with a significant decrease in intraocular pressure (IOP) (Mirakhur and Shepherd, 1985). In the present study, we have compared the effects of propofol on IOP with those of thiopentone in patients receving suxamethonium, and in whom tracheal intubation was performed.

SUMMARY

Changes in intraocular pressure (IOP) were studied in patients given propofol 2.1 mg kg^{-1} (n = 30) or thiopentone 4.9 mg kg^{-1} (n = 30) followed by suxamethonium 1.0 mg kg^{-1} and tracheal intubation. Half the patients in each group received an additional smaller dose of the same induction agent (propofol 1.0 mg kg^{-1} or thiopentone 2.0 mg kg^{-1}) immediately before intubation. Both agents produced significant decreases in IOP which were slightly more marked with propofol. The administration of suxamethonium produced an increase in IOP in all groups, more so in those given thiopentone, in whom it exceeded the control values. Intubation of the trachea produced the greatest increase in IOP, averaging about 25% above control in all groups except in the group given the additional dose of propofol, in whom IOP remained below control values throughout the process of induction and intubation. Ten patients (33%) experienced pain on injection with propofol. A decrease in systolic arterial pressure of more than 30% was observed in 12 patients (40%) receiving propofol, compared with three (10%) of those given thiopentone.

PATIENTS AND METHODS

Sixty adult patients, 16–83 years old, conforming to ASA grades I and II and scheduled to undergo elective ophthalmic surgery, were included in the study after obtaining the approval of the Hospital Ethical Committee, and the informed consent of the patients. Patients with pre-existing increases in IOP (glaucoma), hypertension, obesity (body weight greater than 120% of that expected for age) or those receiving any drugs likely to have an effect on IOP were excluded. Following premedication with diazepam 5–10 mg by mouth, 30 patients each received a dose of either propofol 2.0–2.5 mg kg^{-1} or thiopentone 4.5–5.0 mg kg^{-1} sufficient to induce sleep—as judged by the loss of eyelash reflex and failure to respond to verbal communication. This was followed by suxamethonium 1.0 mg kg^{-1} and the trachea was intubated 2 min later. Half the patients in each group received an additional smaller dose of the same induction agent (propofol 1.0 mg kg^{-1} or thiopentone 2.0 mg kg^{-1}) immediately before intubation.

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IOP was measured using a hand-held applanation tonometer (Perkins, 1965) in the eye not to be operated upon. Baseline (control) values of IOP were obtained before the induction of anaesthesia following instillation of 1% amethocaine. Further measurements of IOP were made after the administration of the propofol or the thiopentone, 1 and 2 min after the administration of the suxamethonium, and 1, 2 and 3 min after the intubation of the trachea. Heart rate and arterial pressure were measured and recorded at the same times using an ECG and an oscillometer (Dinamap), respectively. Note was also made of any pain on injection or any other side effects such as involuntary movements, tremor, hiccups etc. Based on these criteria, the induction of anaesthesia was classified as good, adequate or poor—depending on the observation of no, minor or severe side effects, respectively.

Analysis of variance was applied at each time point to determine the significance of the changes in IOP, arterial pressure and heart rate. When the overall *F* ratio was statistically significant, pairs of means were compared using Student's *t* test.

RESULTS

The patients in the four subgroups were comparable with regard to age, weight and IOP (table I). This table also shows that the average induction doses were 2.1 mg kg^{-1} for propofol and 4.9 mg kg^{-1} for thiopentone. The average induction time was around 40 s, and in the majority the induction agent was injected to a vein on the dorsum of the hand. Values of IOP in the various groups are given in table II, with percentage changes shown in figure 1. The administration of the induction agent produced a significant ($P < 0.0005$) decrease in IOP which averaged around 40% with propofol and 31% with thiopentone: the differences were not significant between the groups. The administration of

TABLE I. *Physical characteristics of patients*

	Propofol		Thiopentone	
	One dose	Two doses	One dose	Two doses
n	15	15	15	15
Age (yr ± SD)	67 ± 12.4	57 ± 21.7	57 ± 19.7	60 ± 20.4
Weight (kg ± SD)	64 ± 8.2	63 ± 9.5	67 ± 9.8	66 ± 10.6
IOP (mm Hg ± SD)	12.1 ± 3.11	13.2 ± 3.08	13.0 ± 4.07	13.1 ± 2.31
Induction dose (mg kg^{-1} ± SD)	2.1 ± 0.25	2.2 ± 0.34	4.8 ± 0.69	5.0 ± 0.51
Duration of induction (s ± SD)	39 ± 4.8	39 ± 6.5	37 ± 5.9	38 ± 4.4
Site of injection				
Hand	13	13	10	14
Antecubital fossa	2	2	5	1

TABLE II. *Intraocular pressures (mm Hg) during induction and intubation (mean ± SD) * Significantly less than respective control* ($P < 0.0005$) *in each group. ** Significantly greater than "after induction" value* ($P < 0.001$) *in each group. † Significantly higher than respective control* ($P < 0.05$–0.001)

	Propofol		Thiopentone	
	One dose	Two doses	One dose	Two doses
Baseline (control)	12.1 ± 3.11	13.2 ± 3.08	13.0 ± 4.07	13.1 ± 2.31
After induction agent	7.6 ± 3.59*	8.0 ± 2.78*	8.1 ± 3.62*	9.2 ± 1.78*
1 min after suxamethonium	10.8 ± 3.49**	12.9 ± 4.27**	13.1 ± 4.21**	13.9 ± 3.83**
2 min after suxamethonium	11.7 ± 4.18**	11.9 ± 3.49**	13.6 ± 4.56**	14.7 ± 3.85**
After 2nd dose of induction agent	—	9.6 ± 3.74*	—	12.0 ± 4.54
1 min after intubation	15.5 ± 4.72†	12.5 ± 4.89	16.3 ± 5.60†	16.5 ± 4.19†
2 min after intubation	13.5 ± 4.26	11.3 ± 4.67	13.7 ± 4.22	13.9 ± 3.03
3 min after intubation	11.4 ± 3.99	9.9 ± 3.93	12.1 ± 4.42	12.9 ± 2.74

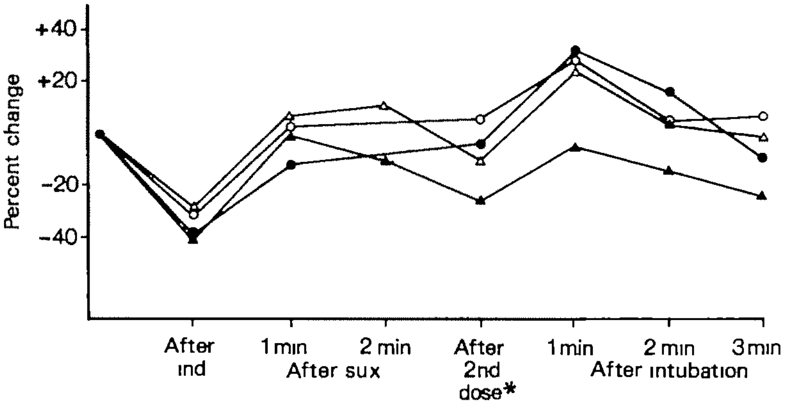

FIG. 1. Percent changes in intraocular pressure during the induction (ind.) of anaesthesia, the administration of suxamethonium (sux.) and the intubation of the trachea. *Second dose of induction agent. ●——● = Propofol one dose; ▲——▲ = propofol two doses; ○——○ = thiopentone one dose; △——△ = thiopentone two doses.

suxamethonium produced an increase in IOP in all groups, the increase being slightly less in those given propofol, in whom the IOP remained less than baseline values in comparison with those receiving thiopentone. The absolute values of IOP were not significantly higher than baseline in any group, although the increase was significant ($P < 0.001$) when compared with the values obtained immediately before the administration of the suxamethonium in all groups. The administration of the second, smaller dose of the induction agent resulted in a decrease in IOP to about 27% below baseline in those given propofol ($P < 0.001$), and by about 8% in those given thiopentone. Tracheal intubation produced the greatest increase in IOP, averaging about 25% above baseline in all groups except that given the additional dose of propofol, in whom the IOP was significantly lower ($P < 0.05$–0.001) in comparison with all the other groups. IOP in the two-dose propofol group always remained less than baseline; the increases were significant ($P < 0.01$) in the other three groups.

Heart rates and systolic arterial pressures are given in tables III and IV. Although the administration of thiopentone tended to increase the heart rate slightly more than propofol, there were no significant differences in absolute heart rate amongst the groups, except in those given the second dose of induction agent, where patients given thiopentone showed a higher heart rate. Systolic arterial pressure decreased signifi-

TABLE III. *Heart rate (beat min*$^{-1}$*) during induction and intubation (mean* ± *SD). Differences are significant between* · *(a) Propofol two doses* v. *thiopentone two doses at 2 min after suxamethonium* (P < *0.05*). *(b) Propofol one dose* v. *thiopentone two doses before intubation* (P < *0.01*). *(c) Propofol two doses* v. *thiopentone two doses after administration of the second dose of induction agents* (P < *0.01*). *(d) Thiopentone one dose* v. *thiopentone two doses before intubation* (P < *0.05*)

	Propofol		Thiopentone	
	One dose	Two doses	One dose	Two doses
Baseline (control)	81±21	78±12	75±18	75±13
After induction agent	88±17	82±11	84±21	90±9
1 min after suxamethonium	92±15	84±12	82±22	92±15
2 min after suxamethonium	87±16	83±11	82±22	92±17
After 2nd dose of induction agent	—	82±12	—	95±15
1 min after intubation	96±19	91±16	91±20	99±16
2 min after intubation	90±17	88±13	92±27	97±14
3 min after intubation	85±13	85±13	88±21	94±12

TABLE IV. *Systolic arterial pressure (mm Hg) during induction and intubation (mean ± SD). Differences are significant between: (a) Propofol two doses* v. *thiopentone two doses at 2 min after suxamethonium* ($P < 0.05$). *(b) Propofol one dose* v. *thiopentone one dose 2 min after suxamethonium* ($P < 0.05$). *(c) Propofol one dose* v. *thiopentone two doses 2 min after suxamethonium* ($P < 0.001$). *(d) Propofol two doses* v. *thiopentone two doses after 2nd dose of the induction agent* ($P < 0.001$). *(e) Propofol two doses* v. *thiopentone two doses at 3 min after intubation* ($P < 0.01$)

	Propofol		Thiopentone	
	One dose	Two doses	One dose	Two doses
Baseline (control)	152±18	152±17	154±22	157±16
After induction agent	124±20	127±18	132±20	143±14
1 min after suxamethonium	120±23	128±16	134±33	145±28
2 min after suxamethonium	124±19	133±17	144±31	158±34
After 2nd dose of induction agent	—	125±15	—	163±30
1 min after intubation	149±27	153±27	169±34	177±31
2 min after intubation	151±29	143±27	165±36	174±26
3 min after intubation	139±31	132±25	154±33	168±22

cantly ($P < 0.01$) soon after the induction of anaesthesia. The systolic pressures were significantly lower ($P < 0.05$–0.005) in those given propofol immediately before and 3 min after intubation. The administration of the second dose of propofol did not result in any further decrease in the average systolic arterial pressure. The average peak heart rates and arterial pressures following intubation were lower in those given propofol, but the differences were not significant.

The incidence of side effects is given in table V. Ten (33%) patients given propofol complained of modest to severe pain on injection. In most, the drug had been injected to a vein on the back of the hand. Forty percent of patients given propofol showed a decrease in systolic pressure of greater than 30% in comparison with 10% of those given thiopentone. This required the administration of 500–1000 ml of lactated Ringer's solution to four patients given propofol. Other side effects were mostly minor in nature. There was no difference in the overall quality of induction in the various groups, nor were there any venous sequelae up to 24 h after injection—although the veins were not solely used for the administration of the induction agents.

DISCUSSION

The findings from the present study confirm the results of previous investigations that the induction of anaesthesia with propofol or thiopentone is associated with useful and significant decreases in IOP, with propofol producing a marginally greater effect (Joshi and Bruce, 1975; Mirakhur and Shepherd, 1985). The present study was, however, designed to assess the effects of these agents on IOP in the face of two factors, the administration of suxamethonium and tracheal

TABLE V. *Side-effects*

	Propofol		Thiopentone	
	One dose	Two doses	One dose	Two doses
Pain on injection (%)	40	27	0	0
Spontaneous movement (%)	—	6.7	20	6.7
Hiccup (%)	6.7	—	—	—
Quality of anaesthesia				
Good	80	73	73	87
Adequate	20	27	27	13
Greater than 30% decrease in arterial pressure (%)	40	40	13	7

intubation, known to produce increases in IOP (Pandey, Badola and Kumar, 1972). It is clear that the stimulus of intubation produces an increase in IOP which is even greater than that observed after the administration of suxamethonium. In spite of an initial decrease, the administration of suxamethonium and intubation of the trachea increased the IOP above the control values in three out of the four groups, the increase being greater in those patients in whom anaesthesia was induced with thiopentone. However, IOP always remained below baseline values when the induction dose of propofol was followed by a smaller second dose of propofol immediately before intubation. The rationale for administering a second dose of the induction agent before intubation was based on the observation that this technique helps to attenuate the increase in intracranial pressure associated with intubation (Unni et al., 1984), and it is known that the pressures in the eye and in the central nervous system are affected similarly by a number of factors. The usefulness of this technique using propofol is further shown by the observation of a rapid decrease in IOP once the stimulating effects of intubation had abated. The lack of protective effect of the second smaller dose of thiopentone is surprising, but may be related to the fact that the administration of thiopentone did not cause such a marked decrease in IOP before intubation. It may also be a result of the fact that propofol, particularly the second dose, produces a deeper and smoother sleep. Part of the beneficial effect on IOP may also be attributable to a greater reduction in systolic arterial pressure seen with this agent.

Other factors such as central venous pressure or carbon dioxide tensions in arterial blood could have affected the results (Hvidberg, Kessing and Fernandes, 1981; Smith, Aass and Nemoto, 1981) However, all patients were horizontal throughout the period of study and ventilation was assisted or controlled as soon as indicated using a non-rebreathing circuit. Moreover, all groups would be similarly affected and, in addition, this was designed to simulate as closely as possible the routine induction of anaesthesia.

It is true that the use of a non-depolarizing neuromuscular blocking drug would not have increased the IOP after the induction of anaesthesia, but suxamethonium was used as a challenge to assess both the effects of propofol and the usefulness of a second smaller dose of induction agent before intubation. Moreover, it is likely that intubation, which is essential in all intraocular surgery, would have produced an increase in IOP anyway. We are, however, studying this technique using non-depolarizing neuromuscular blocking drugs.

Although other side effects of propofol are generally minimal, significant and clinically important hypotension occurs frequently. This is a limitation to its use, particularly in elderly patients. Thus it should be used with discretion, or perhaps avoided, when a decrease in arterial pressure would be particularly undesirable. However, hypotension responded to simple treatment such as the infusion of 500–1000 ml of lactated Ringer's solution.

In conclusion, propofol appears to be a suitable agent with which to induce anaesthesia in ophthalmic surgical patients, particularly if an additional small dose is given immediately before intubation.

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COMPARISON OF THE EFFECTS OF ETOMIDATE AND THIOPENTONE ON INTRAOCULAR PRESSURE

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SUMMARY

The effects of etomidate and thiopentone on intracular pressure were studied in 50 patients of either sex undergoing routine non-ophthalmic surgery. Both drugs decreased intraocular pressure significantly. However, etomidate induced a significantly greater decrease in intraocular pressure than did thiopentone.

Patients with penetrating eye injuries, and patients undergoing emergency ophthalmic surgery in whom intraocular pressure (IOP) is increased may lose intraocular contents—especially at the time of tracheal intubation. Techniques such as precurarization, or the use of non-depolarizing neuromuscular blocking drugs have been advocated to overcome this problem.

Etomidate is a short-acting non-barbiturate i.v. anaesthetic agent. Its administration is associated with cardiovascular stability and only minimal respiratory depression. The untoward effects of etomidate are involuntary muscle movements and pain at the site of injection. It decreases intraocular pressure (Oji and Holdcroft, 1979). Thiopentone also decreases intraocular pressure. The present study was undertaken to compare the decreases in IOP associated with the use of thiopentone or etomidate.

PATIENTS AND METHODS

Fifty patients of either sex (aged 14 yr and above) undergoing elective non-ophthalmic surgery were studied. The patients were selected at random. The procedure was explained in detail and informed consent obtained.

Atropine sulphate 0.6 mg i.m. was given 45 min before the induction of anaesthesia. Lignocaine hydrochloride 4% was instilled to both eyes before induction and IOP was recorded in both eyes (Schiotz Tonometer). Patients were then allotted to receive either thiopentone 4–5 mg kg^{-1} ($n = 25$) or etomidate 0.3 mg kg^{-1} ($n = 25$) at random. IOP was measured at 1, 2 and 3 min after the administration of the induction agent. Antibiotic eye drops (Vanmycetin) were instilled to both the eyes and the eyes covered with sterile cotton pads. Systolic arterial pressure was measured before and after induction. Suxamethonium 1–2 mg kg^{-1} was then given and the trachea intubated under direct vision. Anaesthesia was maintained with 70% nitrous oxide in oxygen.

Patients were observed for 24 h after operation. They were asked about any irritation in the eyes, or excessive watering of the eyes. Eyes were examined for any redness or corneal abrasions.

Statistical analysis was by *t* test.

RESULTS

There were comparable decreases in systolic arterial pressure, after induction, in both groups. In the group receiving etomidate, systolic arterial pressure decreased from 128±16 (mean±SD) mm Hg to 118±13 mm Hg. In the thiopentone group the systolic arterial pressure decreased from 122±27 mm Hg to 116±19 mm Hg (table I).

TABLE I. *Maximum changes in systolic arterial pressure (SAP) (mean ± SD) after etomidate or thiopentone*

Induction agent	SAP (mm Hg) Before operation	SAP (mm Hg) After induction
Etomidate ($n = 25$)	128±15.5	118±13.3
Thiopentone ($n = 25$)	122±26.7	116±18.8

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TABLE II. *Maximum changes in intraocular pressure after etomidate or thiopentone (mm Hg)*

	Before induction		After induction					
			1 min		2 min		3 min	
Induction agent	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
Etomidate								
Mean	15.9	15.9	7.9	7.9	8.0	8.0	7.8	8.0
SD	1.3	1.6	1.0	1.0	1.1	1.7	1.1	1.6
Thiopentone								
Mean	15.3	15.0	10.0	9.8	9.7	9.7	9.8	9.8
SD	1.4	1.0	1.8	1.7	1.8	1.6	1.9	1.8

IOP decreased, in the etomidate group, from 15.9 (±1.3) mm Hg (mean ± SD) to 7.9 ± 1.0 mm Hg, and remained low until the suxamethonium was given (table II). A similar mean decrease in IOP was noted in the thiopentone group (from 15.3 ± 1.4 mm Hg to 10.0 ± 1.8 mm Hg), and this was maintained at the 2nd and 3rd min (table II). The decrease in IOP attributable to etomidate was significantly greater than that associated with thiopentone.

Pupillary changes were seen immediately after the administration of the etomidate. Initial dilatation of the pupils was followed by constriction. No ophthalmic complications were encountered in the 24 h following the procedure.

DISCUSSION

Various factors can alter IOP during anaesthesia. Atropine was the only premedication given to the patients because it does not produce any change in IOP (Eakin and Katz, 1966). Oji and Holdcroft (1969) studied the effects of etomidate on IOP and suggested that the observed decrease in IOP could be the result of the accompanying decrease in the systolic arterial pressure. In the present study the decreases in systolic arterial pressure associated with the administration of thiopentone or etomidate were not significant ($P < 0.01$). However, the decreases in IOP obtained in the present study were significant ($P < 0.001$). Moreover, the decrease produced by etomidate was significantly greater than that produced by thiopentone. Oji and Holdcroft (1969) suggested that the decrease in IOP associated with etomidate (which occurred after 1 min) was primarily the result of an action involving the facilitation of aqueous outflow. We support the possibility of such a mechanism, although a controlled study involving the use of a drug blocking aqueous outflow would be required to confirm this hypothesis.

Thompson and colleagues (1982) also reported a decrease in IOP with etomidate and highlighted the possible influences of central venous pressure, systolic arterial pressure and arterial carbon dioxide tension. The effect of these factors is largely mediated through variations in choroidal blood flow. They also suggested that a secondary action on the production of the aqueous fluid could decrease IOP. However, we believe that such a secondary effect is unlikely to be an important mechanism in the reduction of intraocular pressure because the effects were seen rapidly (within 1 min of the administration of the etomidate). A similar decrease in IOP was seen following the administration of the thiopentone ($P < 0.001$). However, the mean decrease was less than that associated with etomidate. Rubin and Esente (1950) suggested that this decrease in IOP could result from the action of thiopentone on the ocular centre in the diencephalon. We agree more with Duncalf and Weitzner (1963), who suggested that an increase in the outflow of aqueous humor, relaxation of extraocular muscles and peripheral vasodilatation could be the factors causing the decrease in IOP.

Involuntary muscle movements caused by etomidate did not interfere with measurements of IOP. A large vein was used for the administration of etomidate and this reduced the frequency of pain at the site of injection. We made no attempt to determine whether the increase in intraocular pressure, associated with the administration of suxamethonium, was obtunded following the administration of the etomidate or thiopentone. However, it would have been worthwhile considering this point since it would be clinically useful to know whether the initial decrease in intraocular pressure, produced by the etomidate or thiopentone, obtunded, or minimized, the increase in intraocular pressure which usually accompanies the administration of suxamethonium.

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EFFECTS OF INCREASING ENFLURANE CONCENTRATIONS ON INTRAOCULAR PRESSURE

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SUMMARY

The effects of enflurane at various concentrations on intraocular pressure (IOP) were studied. In 15 healthy patients, intubated and mechanically ventilated, IOP was measured the day before surgery, after premedication and during anaesthesia, after administration of 0.5%, 1.0% or 1.5% enflurane. Enflurane in combination with general anaesthesia and controlled ventilation ($P\text{CO}_2$ 4.7–5.3 kPa) caused a significant decrease in IOP. The decrease was more marked (44%) with 1% enflurane than with 0.5% enflurane (21%). The change in IOP was comparable with 1.0% and 1.5% enflurane; however, systolic arterial pressure decreased more with enflurane 1.5%. Increasing the inspired concentration of enflurane from 1% to 1.5% did not appear to be associated with any further decrease in IOP.

During ophthalmic surgery, a variety of anaesthetic techniques are used in an attempt to prevent increases in intraocular pressure (IOP) (Lynch, Wolf and Berlin, 1974). Among the volatile anaesthetics, enflurane is of particular interest (Radtke and Waldman, 1975) since Runciman and colleagues (1978) confirmed that 1% enflurane reduces IOP consistently, whereas halothane, in equipotent concentrations (0.5%), gave unpredictable results. The aim of this study was to define the effects of increasing enflurane concentrations on IOP.

PATIENTS AND METHODS

The study was undertaken in 15 patients (mean age ±SEM: 25.1±1.3 yr; ASA I or II) undergoing plastic or orthopaedic surgery. None of the orthopaedic patients had a tourniquet applied during either anaesthesia or the surgical procedure. Informed consent was obtained from all patients. Patients with previous ophthalmic problems such as glaucoma, or with contraindications to the use of enflurane, were excluded.

The patients were premedicated with hydroxyzine 100 mg i.m. 45 min before anaesthesia was induced with thiopentone 7.5 mg kg^{-1}. Pancuronium 0.1 mg kg^{-1} was administered and, after tracheal intubation, ventilation was controlled using a Logic 06 ventilator delivering a minute volume of 120 ml kg^{-1} with a mixture of 50% nitrous oxide in oxygen. Carbon dioxide tension was measured (capnography) and ventilation was adjusted to maintain $P\text{CO}_2$ between 4.7 and 5.3 kPa. Enflurane was then added to the inspired gas mixture via an open breathing system using a newly calibrated vaporizer (Cyprane Ltd). Three concentrations of enflurane were used successively: 0.5%, 1%, 1.5%, each for 10 min.

The IOP was measured with a Schiotz–Winter tonometer after the instillation of local anaesthetic solution to the conjunctival sac. In all patients, measurements were made on the day before the intervention (control), before the induction of anaesthesia and in association with each enflurane concentration, starting with the lowest and finishing with the highest.

Arterial pressure (sphygmomanometer) and heart rate were recorded initially with the patient awake and then at 5-min intervals and after each

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TABLE I. *Intraocular pressure (mm Hg) and systolic arterial pressure (mm Hg) at varying enflurane concentrations. Compared with control value:* *$P < 0.05$; ***$P < 0.001$. *Compared with 1.0% enflurane:* †$P < 0.01$. *All results are mean ± SEM*

	Control	After premedication	0.5% Enflurane	1% Enflurane	1.5% Enflurane
Intraocular pressure (mm Hg)	19.4±1.1	21.8±1.7	15.7±1.1*	11.1±0.5***	11.6±0.7***
Systolic arterial pressure (mm Hg)	124±3	124±6	114±4	105±4***	97±4***†

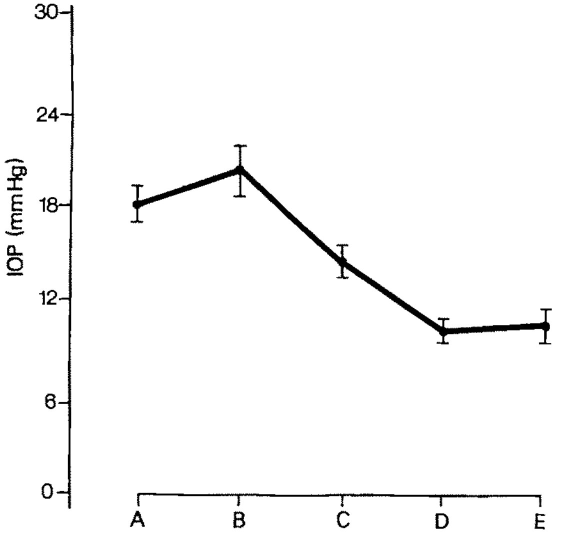

FIG. 1. Changes in intraocular pressure at varying enflurane concentrations. A = Control; B = after premedication; C = 0.5% enflurane; D = 1.0% enflurane; E = 1.5% enflurane.

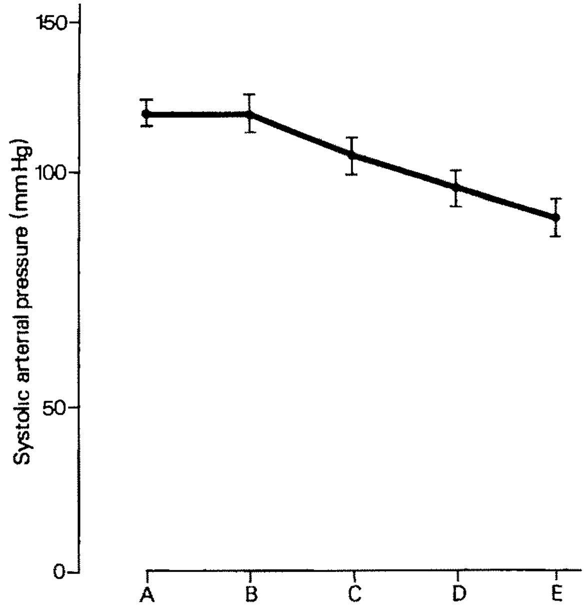

FIG. 2. Changes in systolic arterial pressure at varying enflurane concentrations (see figure 1)

measurement of IOP. All measurements were obtained by the same clinician.

For statistical analysis of the results, analysis of variance and Student's paired *t* test were used. Differences were considered significant when $P < 0.05$.

RESULTS

Results are presented in table I. After premedication, IOP increased slightly, but the difference was not statistically significant. Whatever the enflurane concentration, IOP decreased significantly compared with control values: 21% with 0.5% enflurane ($P < 0.05$); 44% with 1.0% enflurane ($P < 0.001$) and 41% with 1.5% enflurane ($P < 0.001$) (fig. 1). There were significant decreases in IOP between 0.5% enflurane and 1.0% enflurane ($P < 0.001$), and between 0.5% and 1.5% ($P < 0.001$). The IOP values between 1% enflurane and 1.5% enflurane did not achieve significance.

Systolic arterial pressure decreased, but not significantly, after the administration of 0.5% enflurane. Enflurane 1% and 1.5% produced significant decreases in systolic arterial pressure of 15% ($P < 0.001$) and 21% ($P < 0.001$), respectively (fig. 2). The difference in systolic arterial pressure between 1.0% enflurane and 1.5% enflurane was significant ($P < 0.01$).

DISCUSSION

The changes in intraocular pressure observed in this study may be considered to be a result of the administration of the enflurane. Ventilation was controlled under conditions comparable to those used by other workers for this kind of study (Runciman et al., 1978), such conditions ensuring normocapnia, or even hypocapnia (Nunn, 1960). No comparison with any state of anaesthesia in which enflurane was not present was performed, because the aim of this study was to compare three different concentrations of enflurane during anaesthesia. Moreover, previous studies had shown that IOP was not altered much by the other anaesthetic agents used: hydroxyzine (Farnati et al., 1967), thiopentone or pancuronium (Al-Abrak and Samuel, 1974; Runciman et al., 1978). Because the increase in the alveolar concentration of enflurane is rapid in the first few minutes of uptake (Torri et al., 1972), an interval of 10 min between measurements was chosen.

An applanation tonometer would be more accurate than the Schiotz tonometer to measure IOP. However, the main advantage of the tonometer used was its simplicity, and it is still in use in other studies during general anaesthesia (Balamoutsos et al., 1983; Vilardi et al., 1983). To be more accurate and reliable, all the measurements were performed in triplicate and always by the same investigator.

The effects of enflurane on IOP have already been investigated. Radtke and Waldman (1975) reported a decrease in IOP in youths during spontaneous ventilation. In this study, the results may have been influenced by the anaesthetic technique used and by hypercapnia, which tends to increase IOP (Collet, 1960). In conditions comparable to those obtaining in the present study (controlled ventilation, anaesthesia with thiopentone and pancuronium), Runciman and colleagues (1978) established that the administration of 0.5% halothane caused an unpredictable decrease in IOP of 14% whereas enflurane caused a decrease in IOP of 40% of the control values. On the other hand, Presbitero and co-workers (1980) found no relationship between enflurane concentrations and decreases in IOP.

The results of the present study are in agreement with those of Runciman and colleagues (1978). The decrease in IOP was greater with 1.0% enflurane than with 0.5% enflurane, but the increase in enflurane concentration from 1.0% to 1.5% did not change IOP. The mechanisms of the effect of enflurane on IOP are multiple:

(1) Relaxation of intraocular and extraocular muscles; the greater decrease in IOP with enflurane than with halothane could be the result of the neuromuscular effects of enflurane (Lebowitz, Blitt and Walts, 1970).

(2) Decrease in production of aqueous humour and facilitation of its flow (Duncalf, 1975).

(3) Action on the central nervous system, particularly on the hypothalamus, which plays a role in the control of IOP (Presbitero et al., 1980).

(4) Variations of systemic arterial pressure which may alter IOP (Duncalf, 1975; Philajaniemi and Helve, 1977). The decrease of systolic arterial pressure shown in the present study could partly explain the decrease in mean IOP which was, however, much more marked than the change in arterial systolic pressure. The values of systolic arterial pressure remained greater than 90 mm Hg, a value which usually does not affect IOP (Adams and Barnett, 1966).

(5) In our study central venous pressure (CVP) was not monitored, but none of the orthopaedic patients had a tourniquet applied that could have led to changes in CVP. Furthermore, no changes in CVP after induction in comparable conditions of anaesthesia were observed by Runciman and colleagues (1978). A decrease in IOP could result from a decrease in CVP (Jantzen et al., 1986), but increasing the enflurane concentration during controlled ventilation produces an increase in right atrial pressure (Calverley et al., 1978), so the decrease in IOP is probably not explained by changes in CVP.

To conclude, enflurane in combination with nitrous oxide, muscle relaxation and thiopentone, during controlled ventilation and normocapnia, caused a decrease in IOP, and this may decrease the risk of vitreous loss during intraocular surgery; but it does not seem necessary to administer a concentration greater than 1.0%. The increase in the concentration of enflurane from 1.0% to 1.5% did not alter IOP, but decreased arterial pressure. This decrease in arterial pressure, although sometimes desirable, may be hazardous on occasions. The results of the present study were observed in healthy adults. The effects of enflurane on IOP could be different in patients with preoperative modifications of IOP such as glaucoma.

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NALOXONE DOES NOT INFLUENCE BREATHING DURING ISOFLURANE ANAESTHESIA

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SUMMARY

Naloxone influences ventilation, probably by an action on endogenous opioids, in several conditions in which ventilation is reduced or impaired. Ventilatory depression is a feature of anaesthesia; some of the actions of anaesthetic drugs have been attributed to endogenous opioids. Naloxone was given to two groups of patients to investigate the possibility that ventilatory depression might be reversed. Patients breathed isoflurane in oxygen (1.5% end-tidal) or isoflurane in 67% nitrous oxide in oxygen (0.75% end tidal) which are approximately equivalent MAC values. Naloxone 2 mg, i.v. given during surgery had no influence on ventilation or ventilatory timing in either group.

Although naloxone does not influence breathing in normal conscious man (Fleetham et al., 1980), it does influence ventilation in patients with chronic obstructive lung disease (Santiago et al., 1981) or with ventilatory failure (Ayres et al., 1982), and once ventilation has been depressed with diazepam (Jordan, Lehane and Jones, 1980). These effects are attributed to the reversal of the action of endogenous opioids. These substances, or their receptors, have been implicated in the mechanisms of anaesthesia and analgesia: for instance, naloxone influences the analgesic effect of nitrous oxide (Yang, Clark and Ngai, 1980), and increases circulatory and ventilatory output in anaesthetized animals (Arndt and Frey, 1979; Lawson, Waldrop and Eldridge, 1979).

This study was designed to investigate and compare the influence of naloxone on ventilation in patients anaesthetized with isoflurane in oxygen, or in 67% nitrous oxide in oxygen. In the latter group, opioid receptors may be activated. Since opioid drugs have a strong influence on the timing of the ventilatory cycle during anaesthesia (Drummond, 1984) particular attention was paid to this feature. Airway occlusion pressure was measured as a more direct index of ventilatory output.

PATIENTS AND METHODS

The study was approved by the local ethics committee and patients gave their informed consent. Otherwise healthy patients were studied during surgery for varicose veins or inguinal hernia. They received temazepam 20 mg by mouth 1 h before anaesthesia was induced with etomidate 20 mg i.v. The trachea was intubated with the aid of suxamethonium 70 mg i.v. using a plastic tracheal tube (Mallinkrodt), 8.0 mm i.d. for women and 9.0 mm i.d. for men. When spontaneous breathing returned, patients breathed from a T-piece system, through a large-bore tap, a low resistance non-rebreathing valve (Ambu Hesse) and a pneumotachograph (Mercury Electronics F 100 L). The tracheal tube had a narrow integral sampling cannula that opened near its tip to permit the sampling of gas from the trachea. End-tidal samples were taken by intermittent suction on the sampling cannula and passed through an interferometer (Riken). The tracheal tube was connected directly to the measuring apparatus with no abrupt changes in internal diameter or direction of the gas flow. Airway pressure at the valve, and the pneumotachograph pressure, were measured with transducers (Furness MDC micromanometer) and recorded on a u.v. recorder (Bell and Howell). An i.v. infusion was established.

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TABLE I. *Patient details*

Group	Sex	Age (yr)	Height (m)	Weight (kg)
Nitrous oxide	F	55	1.52	64
	M	52	1.88	105
	M	59	1.78	66
	F	53	1.70	88
	F	42	1.68	56
Oxygen	M	47	1.68	65
	F	25	1.80	72
	M	59	1.75	76
	M	42	1.88	98
	F	49	1.61	79

The patients were divided randomly into two groups of five. The first group (O) breathed isoflurane in oxygen and the end-tidal isoflurane concentration was adjusted to 1.5%. The second group (N) breathed isoflurane and 67% nitrous oxide in oxygen and the end-tidal isoflurane concentration was adjusted to 0.75%. This was based on the assumption that 0.7% isoflurane is equivalent to about 70% nitrous oxide (Eger et al., 1972) so that the two groups were at comparable depths of anaesthesia.

Measurements were taken during the surgical procedure, although not within 20 min of the anticipated end of surgery, so that the naloxone would not affect adversely any opioid-induced analgesia that might be required in the immediate postoperative period. A recording was made of airway flow and pressure for three breaths and then the large-bore tap was closed so that inspiration was attempted against an occlusion, for a single breath.

Five separate control measurements were obtained at 1-min intervals. Naloxone 2.0 mg was then given quickly via the i.v. cannula and flushed in with 10 ml of infusion fluid. After 3 min, measurements were repeated at 30-s intervals for 2 min, and then at 1-min intervals for a further 3 min.

The traces were digitized (Terminal Display Systems LC 12) and analysed (BBC B microcomputer) to give values for tidal volumes (V_T), inspiratory and total ventilatory cycle durations, and the minimum airway pressure (P_{min}) and ventilatory times during the occlusion (T_{I_0} and T^{tot}_0). The mean inspiratory flow rate (V_T/T_I) and rate of decrease in airway pressure during occlusion (P_{min}/T_{I_0}) were also calculated for each breath. Mean values of these measurements were calculated for the control period and for the measurements taken between 3 and 5 min after naloxone.

Paired and unpaired *t* tests were used as appropriate for statistical comparison (Campbell, 1974).

RESULTS

The characteristics of the patients studied are shown in table I. The groups did not differ significantly.

The mean values for the ventilatory variables in

TABLE II. *Measurements of breathing pattern before and after administration of naloxone in the two groups.* T_I = *duration of inspiration*, T^{tot} = *ventilatory cycle duration*, V_T = *tidal volume*, $\dot{V}_I$ = *minute volume*

	Before naloxone				After naloxone			
	T_I (s)	T^{tot} (s)	V_T (ml)	$\dot{V}_I$ (ml min^{-1})	T_I (s)	T^{tot} (s)	V_I (ml)	$\dot{V}_I$ (ml min^{-1})
Isoflurane/ nitrous oxide	0.98	2.26	235	6240	1.01	2.34	250	6410
	1.39	4.41	341	4640	1.51	4.73	392	4970
	1.19	3.07	232	5430	1.00	2.91	285	5880
	0.95	2.03	211	6240	0.98	2.04	237	6970
	1.04	2.38	266	6710	1.03	2.52	213	5070
Mean	1.11	2.83	257	5850	1.14	2.91	275	5860
SD	0.18	0.96	51	820	0.22	1.07	70	860
Isoflurane/ oxygen	0.87	2.45	240	5880	0.98	2.61	255	5860
	0.86	2.31	343	8870	0.87	2.41	287	7140
	0.93	2.34	312	8000	1.04	2.65	282	6380
	0.93	2.00	360	10800	0.84	1.84	261	8770
	1.21	3.55	261	4410	1.24	3.78	300	4760
Mean	0.96	2.53	303	7590	1.00	2.66	277	6580
SD	0.14	0.59	52	2507	0.15	0.71	19	1498

TABLE III. *Pressure and timing of occluded breaths before and after naloxone*

	Before naloxone			After naloxone		
	TI_0 (s)	T^{tot}_0 (s)	P_{min} (cm H_2O)	TI_0 (s)	T^{tot}_0 (s)	P_{min} (cm H_2O)
Isoflurane/	0.87	2.33	16.3	0.90	2.22	17.4
nitrous	1.33	4.41	14.1	1.43	4.87	15.5
oxide	1.08	2.95	6.4	1.00	2.75	6.4
	0.96	2.12	11.5	0.98	2.17	13.5
	1.00	2.35	9.4	0.99	2.31	9.0
Mean	1.05	2.83	11.5	1.06	2.86	12.4
SD	0.17	0.93	3.9	0.21	1.14	4.6
Isoflurane/	0.84	2.45	12.3	0.93	2.54	12.1
oxygen	0.70	2.32	11.8	0.72	2.38	9.1
	0.80	2.34	10.8	0.94	2.78	10.6
	0.80	2.00	30.6	0.69	1.58	21.8
	1.11	3.55	11.0	1.11	3.83	13.0
Mean	0.85	2.53	15.30	0.88	2.62	13.3
SD	0.15	0.59	8.57	0.17	0.81	5.0

each patient, for the control period and the period 3–5 min after naloxone, are given in table II.

There were no statistical differences between the groups in any variable. Naloxone did not cause a statistically significant change in any variable. In particular, T^{tot} did not become less, nor did ventilation increase. No consistent trend was seen in the measurements taken later than 5 min after the injection.

The mean values of TI_0 and of T^{tot}_0 did not change in either group; nor did the values of occlusion pressure (table III).

DISCUSSION

Methods

Patients were studied when anaesthesia was stable, towards the end of surgery. Because of the possiblity that naloxone would interfere with the action of opioids given to relieve pain after the operation, the naloxone was given more than 20 min before the expected end of the surgical procedure. During this part of the operation, the surgical stimulus was relatively constant and did not involve incision or suturing of the skin. However, the depth of breathing in individual patients did vary from time to time, more than in patients who have had a combined regional and general anaesthetic. With the method of end-tidal sampling and analysis used, the response time of the interferometer was slow (95% response in 30 s), but was adequate to follow the slow changes in end-tidal concentration resulting from adjustment of the inspired isoflurane concentration. The end-tidal concentrations chosen were based on the estimate of equivalent anaesthetic potency described by Eger and colleagues (1972)—that 70% nitrous oxide is equivalent to 0.75% isoflurane. Because of the limits of accurate adjustment of end-tidal isoflurane (±0.1%), no account was taken of the variation of MAC with age.

This study was designed to observe the effects of naloxone given during surgery. It would have been of interest to study the effect of naloxone given to patients who were anaesthetized but not subjected to surgical stimuli, such as during combined regional and general anaesthesia. However, investigation of this possibility would have doubled the size of the study. Since clinical experience suggests that the administration of opioids during anaesthesia, and in association with surgical stimuli, has a clear influence on the pattern of ventilation, this possibility was considered less likely. Surgery causes an increase in ventilation (Eger et al., 1972) and this is partly the result of an increase in carbon dioxide production (France et al., 1974). Consequently, the assessment of the degree of ventilatory depression that has been caused by the anaesthetic is difficult, and comparison with patients before anaesthesia is not exact. Nevertheless, the findings of Eger and his co-workers (1972) suggest that ventilation remains depressed by isoflurane anaesthesia despite the stimulatory effect of surgery. This stimulation could possibly offset the influence of the endogenous opioids. However, in the presence of surgery, it is also possible that the reversal of the effects of the endogenous opioids would have a more obvious effect, and that surgical stimulation is necessary to cause the release of endogenous opioids. Waldrop, Eldridge and Millhorn (1983) found that a brief painful stimulus in anaesthetized cats caused ventilatory stimulation that decreased over about 5 min and was followed by a period of depression, lasting up to 1 h, that could be reversed by naloxone. In other circumstances, painful stimuli may have to be administered for much longer before endorphin-mediated analgesia becomes apparent. Nevertheless, the present study was limited by the duration of the stimulus applied, and the naloxone was not given until there had been the greatest possible time available for endorphin activation.

The time chosen for assessment of the possible effects of naloxone (3–5 min after injection) was based on clinical experience with the reversal of opioid drugs in patients, and assumes that naloxone acts on endogenous opioid receptor sites as rapidly as it does on the sites of action of administered opioids. No trends were seen to suggest that any effect took longer to become manifest.

Especial attention was paid to measuring the timing of breathing, as opioids influence timing particularly (Drummond, 1984). Occlusion was used to assess the timing of the ventilatory cycle in the absence of change in lung volume—which may influence timing reflexly—but no effect of naloxone was seen on the timing of the occluded breaths. Occlusion can also be used to measure the output of the ventilatory centre. However, although naloxone reduces the depression of the ventilatory responses to carbon dioxide in volunteers given diazepam, there was no change in occlusion pressure responses in these volunteers (Jordan, Lehane and Jones, 1980). However, in that study by Jordan and colleagues, a much larger dose of naloxone was used (16 mg) and it is possible that non-specific effects could have been caused by the large dose. In the present study, naloxone 2 mg did not influence ventilatory output—neither inspiratory flow (V_T/T_I) nor occlusion pressure. In patients with lung disease, however, naloxone, in the same dose as in the present study, has been shown to increase responses during loaded ventilation (Santiago et al., 1981). In anaesthetized cats, naloxone can increase ventilatory output (Lawson, Waldrop and Eldridge, 1979; Waldrop, Eldridge and Millhorn, 1983).

The influence of naloxone on other aspects of anaesthesia is controversial, since Finck, Ngai and Berkowitz (1977) first suggested that general anaesthesia could be reversed by naloxone. The analgesic effect of nitrous oxide in man is influenced by naloxone in moderate (Gillman, Kok and Lichtigfield, 1980) or large (Yang, Clark and Ngai, 1980) doses. Another measure of anaesthesia, the righting reflex, is not affected by the administration of naloxone to rats anaesthetized with nitrous oxide (Smith, Wilson and Miller, 1978). The anaesthetic effect of halothane may be reduced (Arndt and Frey, 1979) or not affected (Bennett, 1978; Harper et al., 1978) by naloxone. Anaesthesia with thiopentone, nitrous oxide and halothane in man does not influence CSF concentrations of β-endorphin (Way et al., 1984) although, in the rat, prolonged anaesthesia with nitrous oxide decreases the density of opioid receptors in the brainstem (Ngai and Finck, 1982).

Interpretation of many of the studies involving naloxone may be affected by the ability of naloxone, when given in large doses, to act on brain mechanisms other than the opioid system (Sawynok, Pinsky and Labella, 1979).

In conclusion, there is some evidence that ventilatory output may be increased in some circumstances by naloxone, and that some of the effects of anaesthetic drugs, particularly those of nitrous oxide, can be reduced by naloxone. However, the present study was not able to demonstrate that naloxone influenced ventilatory pattern or output in patients anaesthetized with isoflurane, with or without nitrous oxide.

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FETOTOXIC POTENTIAL OF GENERAL ANAESTHESIA IN RELATION TO PREGNANCY

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SUMMARY

Fifty-three infants with neural tube defects and 97 with other major congenital abnormalities have been reviewed. In only one case did the mother receive an anaesthetic before or during pregnancy and this anaesthetic is unlikely to have played any part in the outcome. The anaesthetic history was recorded for 471 mothers who booked consecutively for their confinements. Seventy-two women received 76 anaesthetics, 70 before the last menstrual period and six during pregnancy. The corrected annual incidence of anaesthesia was about 20% (14% related to fertility). There were no fetal abnormalities, but two miscarriages in the women anaesthetized during pregnancy. There was one abnormal baby delivered to a women anaesthetized more than 12 weeks before the last menstrual period.

Although there are conflicting reports of the teratogenic effects of volatile anaesthetic agents in laboratory animals, there is firm evidence that nitrous oxide is teratogenic in the rat. This was first reported by Fink, Shepard and Blandau (1967) who administered 70% nitrous oxide to rats for 48 h during the period of organogenesis. Lane and colleagues (1980) confirmed the observation, but found no such effect with xenon, an anaesthetic of comparable potency. Further confirmation was obtained by Keeling and co-workers (1986) who showed that certain effects could be partially reversed by pretreatment with folinic acid. Thus there seems no doubt that nitrous oxide is teratogenic in the rat and, at least in part, this appears to be because of interference with the metabolism of folate, a known biochemical effect of nitrous oxide.

Nitrous oxide can interfere with thymidine synthesis following administration of nitrous oxide to man for as little as 2 h (Amos et al., 1982). Since thymidine is an essential base of deoxyribonucleic acid (DNA), there is a theoretical basis for nitrous oxide being fetotoxic in man. To investigate this possibility we have undertaken a retrospective study of the incidence of anaesthesia in women delivering and miscarrying abnormal babies in the Obstetric Unit of Northwick Park Hospital, which has approximately 3250 deliveries per year.

We have also undertaken a study to determine the incidence and outcome of general anaesthesia during pregnancy and in the year preceding booking into the antenatal clinic at Northwick Park Hospital.

PATIENTS AND METHODS

Retrospective study

We reviewed all pregnancies producing major congenital abnormalities in the years 1982–1984. In addition, all pregnancies in the years 1977–1984 resulting in a child with a neural tube defect, including miscarriages and terminations, were studied. Information was obtained by inspection of the obstetric records of each individual mother. Records could not be traced in six cases.

Study of the incidence and outcome of anaesthesia

Over a 2-month period, 471 mothers booking consecutively at the antenatal clinic were asked to give details of any anaesthetics given in the 12-month period preceding booking. Clinical details

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TABLE I. *Major congenital abnormalities (other than neural tube defects and Down's syndrome) in the retrospective series.* * *Skeletal abnormalities, extra digits etc. Goldenhaus Syndrome, DeLange Syndrome, Robinow Syndrome etc.*

	1982	1983	1984	Totals
Total No. of pregnancies:	3158	3234	3377	9769
Spontaneous abortions	0	3	2	5
Other CNS	0	2	0	2
CVS	8	13	4	25
Cleft palates	4	4	5	13
Gut	6	6	3	15
Genito urinary	0	5	8	13
Other*	3	5	16	24
Totals	21	38	38	97

were obtained from case notes where necessary. Each mother was then followed until delivery, when the condition of the infant was recorded.

RESULTS

Retrospective study

There were 53 infants with neural tube defects (25 with anencephaly and 28 with spina bifida) out of a total booking of 26222 pregnancies (2.02/1000). Only one mother received a general anaesthetic during or immediately before pregnancy. She had a previous history of four mid-trimester miscarriages and a Shirodkar suture was inserted under general anaesthesia at 12 weeks gestation. During routine scanning at 16 weeks gestation she was found to be carrying a fetus with spina bifida and the pregnancy was subsequently terminated. As the anaesthetic was administered after the organogenic period relevant to spina bifida, it was unlikely to have played any part in the outcome.

There were 97 other major congenital defects during the years 1982–1984 (table I). None of the mothers received an anaesthetic during or just preceding her pregnancy.

Study of the incidence and outcome of anaesthesia

Seventy-two of the 471 mothers received 76 anaesthetics in the year before first attendance at the antenatal clinic, an annual incidence of 16.1% (table II). Of these, 70 anaesthetics were administered to 66 women before the last menstrual period (LMP) (table II). Six mothers were anaesthetized during pregnancy, two at the time of the LMP and four between 11 and 14 weeks gestation (table III).

The 399 women who were not anaesthetized

TABLE II. *Anaesthetics administered before and during pregnancy in the second series. LMP = last menstrual period*

	No. of pregnancies	Outcome
No anaesthetic	399	*8 abnormal babies* 3 talipes 1 reduction deformity of left hand and deformed left ear 1 double thumb 1 13Q chromosomal defect 1 neural tube defect 1 ventricular septal defect
Anaesthetic 12 weeks before LMP	52	*1 abnormal baby* extra digit 1 miscarriage 1 stillbirth 4 lost to follow-up
Anaesthetic 12–4 weeks before LMP	13	No abnormal babies
Anaesthetic < 4 weeks before LMP	5	No abnormal babies
Anaesthetic after LMP	6	See Table III
Total	76 anaesthetics administered to 72 out of 471 women	

produced eight abnormal fetuses or babies (20/1000), including one with spina bifida (table II). The 66 women who were anaesthetized before the LMP produced one abnormal baby, one still birth and one miscarriage with normal pathology. Four babies could not be traced as the mothers had moved out of the area. They last attended the antenatal clinic at 16, 17, 23 and 34 weeks gestation, respectively.

The six mothers who received an anaesthetic during pregnancy delivered four normal babies (table III). Two women miscarried, one after an anaesthetic for insertion of a Shirodkar suture at 14 weeks gestation. She had a previous history of early spontaneous labour and miscarried 5 weeks after the anaesthetic. The second mother had an appendicectomy at 11 weeks gestation and was found to have a missed abortion when she booked into the antenatal clinic at 16 weeks. Both fetuses were found to be normal on pathological examination.

The 471 women were comparable demographically by age to the population attending the Northwick Park Obstetric Unit (table IV) in 1983.

TABLE III. *General anaesthetics administered during pregnancy in the second series. *Fetal pathology demonstrated to be normal. Thio. = thiopentone; Sux. = suxamethonium; Panc. = pancuronium; Enf. = enflurane; Atrac. = atracurium; Fen. = fentanyl; Hal. = halothane*

Gestational age (weeks)	Indication for anaesthesia	Anaesthesia given	Outcome
11/40	Appendicectomy	Thio. Sux. Panc. N_2O: O_2: Enf.	Missed abortion 16/40*
11/40	Shirodkar suture	Thio. Sux. Atrac. N_2O: O_2: Fen.	Normal
11/40	Shirodkar suture	Thio. N_2O: O_2: Hal.	Normal
14/40	Shirodkar suture	Thio. N_2O: O_2:Hal.	Spontaneous abortion 19/40*
0	D & C	Thio. N_2O: O_2: Enf.: Fen.	Normal
0	Dental extractions	Administered elsewhere Record not traced	Normal

TABLE IV. *Demography of sample in second series compared with population*

	Age (yr)						
	⩽ 19	20–24	25–29	30–34	35–39	⩾ 40	Total
Age (numbers)							
No anaesthetic given	8	92	163	99	34	3	399
Anaesthetic given	3	11	30	20	7	1	72
Total	11	103	193	119	41	4	471
Age (%)							
No anaesthetic given	2.0	23.1	40.9	24.8	8.5	0.8	100
Anaesthetic given	4.2	15.2	41.7	27.8	9.7	1.4	100
Total	2.3	21.9	41.0	25.3	8.7	0.8	100
Northwick Park Hospital Obstetric Unit Population (1983)	4.3	21.3	38.3	25.8	9.1	1.2	100

TABLE V. *Indications for anaesthesia before last menstrual period in the second series*

	No. of anaesthetics	% of total
Termination of pregnancy	6	8.6
Dilation and curettage	16	22.8
Evacuation of retained products of conception	19	27 2
Lower segment Caesarean section	4	6.0
Other gynaecological procedures	3	4.0
Subtotal (obstetric and gynaecological)	48	68.6
Dental	7	10.0
Miscellaneous	15	21.4
Total	70	100.0

DISCUSSION

In 150 infants born with spina bifida or major congenital abnormality, none of these defects could be attributed to an anaesthetic administered to the mother during or immediately before pregnancy. This does not disprove the possibility that anaesthetics, and nitrous oxide in particular, can be fetotoxic in the human species, but it suggests that anaesthesia is not a major aetiological factor.

We thought that this might be the result of few anaesthetics being given to this group of comparatively healthy women. However, this view was not supported by the prospective study, in which the incidence of anaesthesia was 16.1% during the 12 months before first attendance at the antenatal clinic.

The 70 anaesthetics given during the period of approximately 9 months before the start of pregnancy corresponds to an annual incidence of anaesthesia of about 20%. Although no precise figures are available, it seems likely that the national incidence of anaesthesia in the U.K. is about 5% (10000 per annum in the average district of 200000 (Report, 1978)). Thus the incidence in this group of relatively healthy, younger women appeared to be about four times the national average. This apparent anomaly is explained by the fact that nearly 70% of the anaesthetics were related to fertility (table V).

During pregnancy, the six anaesthetics (1.3% of mothers) corresponded to an annual incidence of only 1.7%, which is well below the average for the general population and one-tenth the incidence for the 9 months preceding pregnancy. The incidence of surgery during pregnancy in our small series is in line with the much larger series of Shnider and Webster (1965) who reported surgery in 1.6% of pregnancies, although less than one-half the operations were under general anaesthesia (table VI). Brodsky and colleagues (1980) reported surgery under general anaesthesia

TABLE VI. *Summary of published surveys of surgery and anaesthesia during pregnancy*

		Operations		General anaesthetics		
Reference	No. patients	Total	1st Trimester	Total	1st Trimester	Conclusions
Smith (1963)	18 503 pregnancies	67	10	24	5	No fetal abnormalities in offspring of women who had surgery during pregnancy
Shnider and Webster (1965)	9073 deliveries	147	47	60	21	"No greater incidence in birth defects in surgical as compared to non-surgical patients." (5.4% compared with 6% control). Premature delivery rate increased to 8.8%. Perinatal mortality increased to 7.5% (control 2%)
Brodsky et al. (1980)	12 929	Not stated		287	187	No increase in incidence of congenital abnormalities in live offspring. Significant increase in spontaneous abortion rate following surgery in first trimester
Duncan, Pope and Cohen (1985) (abstract only)	Not stated	2565	Not stated	Not stated		No increase in incidence of congenital abnormalities compared with matched controls. Significant increase in spontaneous abortion rate following general anaesthesia—10.9%. (Control 6.5%)

during the first two trimesters in 2.2% of pregnancies. A very much lower incidence of surgery during pregnancy was reported by Smith (1963), who found only 0.36%, and during the first trimester the incidence was only 0.13%.

The high incidence of miscarriage following anaesthetics administered during the first trimester (two out of six in this study) is well known (Brodsky et al., 1980; Duncan, Pope and Cohen, 1985). Stress or the condition requiring the anaesthetic are more than sufficient to explain the high miscarriage rate without the need to implicate the anaesthetic itself.

In the study of the incidence and outcome of anaesthesia, no mother who had received an anaesthetic during pregnancy or in the period of approximately 9 months before first attendance at the ante-natal clinic was delivered of an infant with a major congenital abnormality. Although this part of the study has indicated an unexpectedly high incidence of anaesthesia in childbearing women, it is much too small to assess the possibility that anaesthesia may be fetotoxic. However, the studies listed in table VI are unanimous in their view that no positive relationship has been demonstrated between either anaesthesia or surgery and fetal abnormalities. Slater (1970) reported delivery of a normal baby to a woman who had received multiple anaesthetics during pregnancy, although nitrous oxide was included only in the first. Shnider and Webster (1965) took the cautious view that data from a much larger number of pregnant surgical patients must be collected before the effects of anaesthetic drugs on the human fetus are known. However, the unanimity of the substantial body of evidence in table VI, together with the negative findings of the present study, make it increasingly unlikely that there is a significant risk to the fetus in the administration of an anaesthetic in early pregnancy. The increased likelihood of miscarriage is explicable without implicating the anaesthetic itself. The present epidemiological evidence does not appear to provide grounds for recommending termination of pregnancy in a women who is anaesthetized in early pregnancy.

Two aspects of the problem give grounds for caution. First, the period of critical organogenesis is very short, and there is still a paucity of information regarding anaesthetics administered at this time, although this may be resolved in the full publication of the data of Duncan, Pope and Cohen (1985). Second, for reasons outlined in the introduction, there can be no doubt that nitrous oxide has fetotoxic potential. We believe that this point outweighs the epidemiological findings of ourselves and others. Therefore, in our view, it seems inadvisable to administer nitrous oxide to any woman known to be in early pregnancy. In reaching this conclusion we are influenced by the fact that satisfactory alternatives are freely available and there can be few such patients for whom nitrous oxide is really essential. It seems likely that folinic acid (30 mg twice daily) would provide protection in such patients (Keeling et al., 1986), and it is known to restore normal thymidine synthesis in patients who have received a prolonged administration of nitrous oxide (O'Sullivan, et al., 1981; Amos et al., 1984; Kano et al., 1984).

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Note added in proof

Since this paper was accepted for publication, additional evidence of lack of fetotoxicity of nitrous oxide in pregnant women has been provided by Aldridge and Tunstall (1986), Crawford and Lewis (1986) and Park, Fulton and Shelly (1986). The full paper of Duncan and colleagues has appeared (1986). There is now strong evidence that the risk in practice, if present at all, can be only very small.

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DOUBLE-BLIND STUDY OF THE REVERSAL OF MIDAZOLAM-SUPPLEMENTED GENERAL ANAESTHESIA WITH RO 15-1788†

E. ALON, L. BAITELLA AND G. HOSSLI

SUMMARY

The actions and side effects of the benzodiazepine antagonist Ro 15-1788 were evaluated in a randomized double-blind clinical study in which midazolam was used as an anaesthetic agent. Sixty women who underwent laparoscopy were treated with Ro 15-1788 or with placebo after the surgical procedure. Ro 15-1788 reversed the hypnotic effect of midazolam within a few minutes. The patients were alert, co-operative, oriented and had good recall of events after awakening. The effects were statistically better than placebo for up to 30 min after administration. Arterial pressure and heart rate remained stable and there were no significant side effects. The availability of Ro 15-1788 allows effective reversal of midazolam when this is used during general anaesthesia.

Several studies in animals have shown that the specific benzodiazepine antagonist Ro 15-1788 is highly effective in antagonizing the central effects of benzodiazepines by competitive inhibition (Möhler and Richards, 1983; Little and Bichard, 1984). Studies in healthy volunteers, and in patients, have shown that Ro 15-1788 can reverse benzodiazepine-induced sedation without producing toxic side effects (Darragh et al., 1982; Lauven et al., 1985). The purpose of this study was to evaluate the actions of Ro 15-1788 used to reverse midazolam given as part of a general anaesthetic technique for laparoscopy.

PATIENTS AND METHODS

Sixty women (ASA grades I and II) who were to undergo laparoscopy gave informed consent for inclusion in the study. Exclusion criteria were pregnancy, drug hypersensitivity or addiction to benzodiazepines. All patients were premedicated with midazolam 7.5 mg by mouth and anaesthesia was induced with midazolam 0.2 mg kg^{-1}. Suxamethonium was given to facilitate tracheal intubation. Anaesthesia was maintained with 50% nitrous oxide in oxygen and 0.6–1.5% enflurane. Supplements of midazolam 0.1 mg kg^{-1} were given when needed. Neuromuscular blockade was obtained with atracurium. At the end of surgery the enflurane and nitrous oxide were discontinued and neuromuscular blockade antagonized with neostigmine. After extubation of the trachea, 2 ml of a solution containing Ro 15-1788 0.2 mg or placebo was injected. Increments of 1 ml were given every 30 s until the patient was awake or a total of 10 ml had been given. The study was double-blind and patient allocation was random.

The patients were assessed before, and 5, 15, 30, 60 and 120 min after injection. The degree of sedation was graded on a scale of 0–3 (0 = sleepy not arousable; 1 = sleepy but arousable; 2 = drowsy and 3 = alert). Co-operation and comprehension, evaluated by orders to raise the head and to shake hands, were graded on a scale of 0–2 (0 = no execution of the order; 1 = imitation only and 2 = execution of the order). Orientation was graded from 0 to 2

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according to the patient's awareness of the day of the week and where she was (0 = disorientation; 1 = orientation in time *or* in space and 2 = orientation in time and in space). Amnesia (0 = none; 1 = slight; 2 = moderate and 3 = marked amnesia) was tested by showing the patients pictures and evaluating subsequent recall.

Arterial pressure, heart rate, side effects (graded as mild, moderate and severe) and the need for analgesics during the first 24 h after surgery were also monitored. Subjective assessment of awaking was evaluated 1, 2 and 4 h after injection and graded on a 4-point scale (0 = poor; 1 = satisfactory; 2 = good and 3 = excellent awakening).

Results were analysed using the two sided Mann–Whitney *U* test for evaluating the efficacy of Ro 15-1788 and for the haemodynamic variables. Fischer's exact test was used to compare the side effects. Values were considered significant when $P < 0.05$.

RESULTS

Table I shows that the two groups of patients were comparable in respect of age, weight and height as well as duration of operation and of anaesthesia. The dose of midazolam (mean ± SD) used was 17.3 mg ± 6 in the test group and 16.6 mg ± 4.6 in the placebo group. In both groups midazolam 0.27 mg kg^{-1} was required. Figure 1 shows the results in the two groups. Before the injection of Ro 15-1788 there was no difference between the groups: all patients were asleep, unrousable and

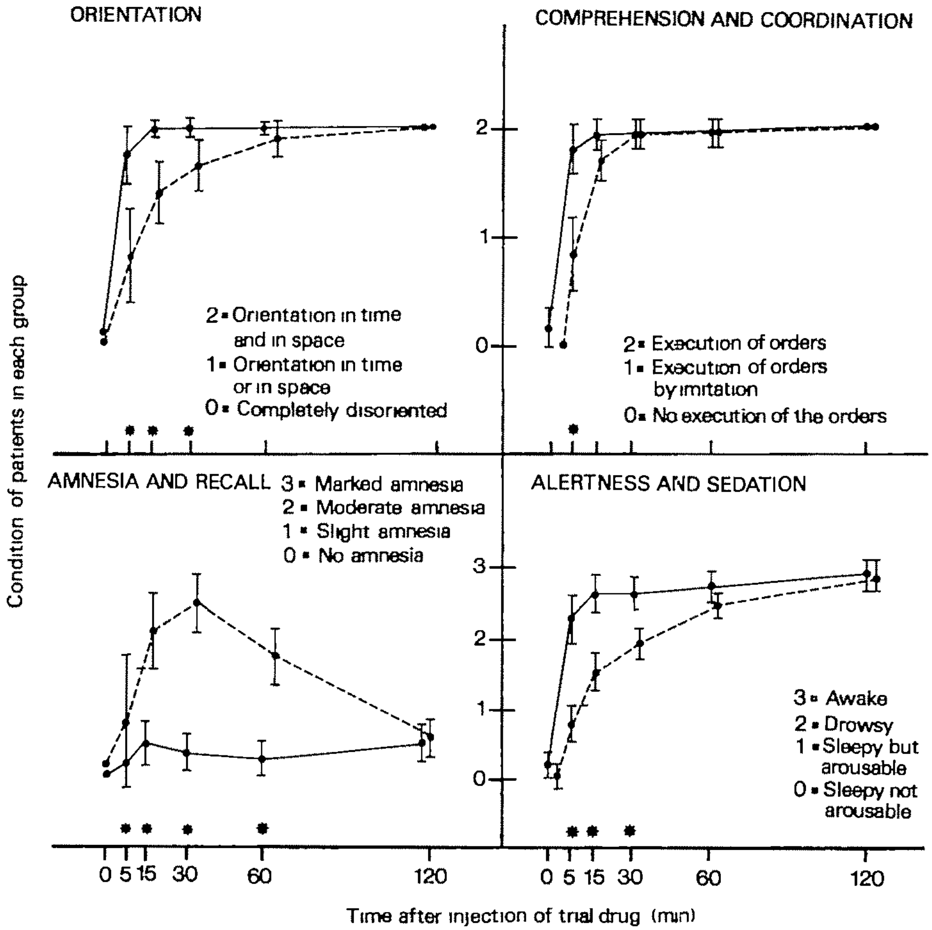

FIG. 1. Patients' clinical condition after injection of trial drug or placebo (mean ± confidence intervals). *Statistically significant ($P < 0.05$). ●——● = Ro 15-1788; ●---● = placebo.

TABLE I. *Details of patients included in the study, duration of surgery and duration of anaesthesia in both groups of patients (mean ± SD)*

	Ro 15-1788	Placebo
Age (yr)	30.7 ± 6.3	35.9 ± 6.8
Weight (kg)	62.0 ± 22.5	60.2 ± 9.5
Height (cm)	157.8 ± 16.8	164.2 ± 6.7
Duration of surgery (min)	38.4 ± 15.7	43.0 ± 15.1
Duration of anaesthesia (min)	56.7 ± 16.9	58.3 ± 14.6

TABLE II. *Side effects after injection of trial drugs in both groups of patients. *Statistically significant difference* ($P < 0.05$)

Side effects	Ro 15-1788	Placebo
Nausea*	11	3
Vomiting	5	4
Tremor	6	4
Involuntary movements	5	4
Headache	1	3

unco-operative (graded 0). Orientation and amnesia were therefore graded 0. Five minutes after the injection the differences between the groups were statistically significant and at 15 and 30 min the patients given Ro 15-1788 were fully awake, co-operative, oriented in time and space and had no amnesia. In contrast, patients who received placebo remained sleepy, unco-operative and disoriented, with slight to moderate amnesia. By 2 h, performance was similar in both groups: all patients were awake. The amount of Ro 15-1788 required varied between 0.3 and 1 mg (mean dose 0.6 mg; SD 0.27).

Systolic and diastolic arterial pressures and heart rate remained stable and did not differ significantly between the two groups. Mild to moderate pain at the site of i.v. injection was reported by eight patients who received Ro 15-1788 and five in the placebo group, a difference which was not statistically significant. No local irritation and no signs of thrombophlebitis were observed in any of the patients. Side effects are shown in table II. The difference between the groups was statistically significant only for nausea, which was graded as only mild or moderate. The postoperative requirement for analgesics was the same in both groups.

All patients reported good to excellent subjective impressions of awakening.

DISCUSSION

This study was undertaken to evaluate Ro 15-1788 and its side effects when given after midazolam-supplemented general anaesthesia. Previously, Lauven and colleagues (1985) administered Ro 15-1788 10 mg i.v. in the presence of a stable concentration of midazolam and demonstrated its prompt effect in an open study. Doenicke and colleagues (1984) showed that Ro 15-1788 0.1 mg kg^{-1} could antagonize an anaesthetic dose of flunitrazepam. This study demonstrated that Ro 15-1788 0.01 mg kg^{-1} could antagonize an anaesthetic dose of midazolam.

The effectiveness of Ro 15-1788 was demonstrated by comparing with placebo its effect on alertness, orientation, comprehension of and cooperation with commands, and recall at the end of anaesthesia. The results indicated that recovery was much faster after the administration of Ro 15-1788. No rebound effects were encountered, probably because of the relatively small amount of benzodiazepine administered. Reports on patients comatose as a result of benzodiazepine intoxication have shown that repeated doses of Ro 15-1788 may be required (Geller, Niv and Silbiger, 1985).

In an animal experiment Glisson and Falinski (1984) showed that Ro 15-1788 reversed the effect of midazolam on catecholamines without adversely affecting haemodynamic stability and, in the present study, haemodynamic stability was maintained. Local tolerance of the drug was good and no potentially serious side effect occurred. There was more nausea in the Ro 15-1788 group and there were a few patients in both groups who reported a mild or moderate degree of tremor and involuntary movement. These results suggest that Ro 15-1788 may be a useful addition to the armamentarium of any anaesthetist using benzodiazepines.

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REVERSAL OF MIDAZOLAM SEDATION WITH ANEXATE

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SUMMARY

Anexate (Ro 15-1788) a specific benzodiazepine antagonist, was assessed for its action in reversing midazolam-induced sedation. Sixty-five patients undergoing prostatic surgery under subarachnoid anaesthesia received midazolam for intraoperative sedation (mean dose 16 mg) followed by either active drug (anexate) or placebo given as a randomized, double-blind i.v. injection. The anexate dose sufficient to reverse sedation (0.36 ± 0.09 mg), produced immediate and dramatic improvements in ability to comprehend and obey commands, in orientation in time and space and in degree of anterograde amnesia. These changes remained significantly different from the control group for 60 min after injection. There was no effect on arterial pressure, heart rate or ventilatory rate and no anxiety states were observed. After initial complete awakening, sedation increased gradually in drug-treated patients, while in the control group, sedation scores and cognitive testing scores all diminished over the 4-h study period. Anexate used in doses up to 0.5 mg provided safe and effective antagonism of midazolam-induced sedation in a clinical setting.

The imidazobenzodiazepine derivative Ro 15-1788 (anexate) was first described by Hunkeler and colleagues (1981). Studies in animals and human volunteers have shown this compound to be an effective specific antagonist of the behavioural, neurological and electrophysiological effects of benzodiazepines (Darragh et al., 1981; Polc et al., 1981) which binds with high affinity (K_D = 0.9 nmol litre^{-1}) to central benzodiazepine receptors (Mohler and Richards, 1981). In man, this drug is devoid of the typical behavioural effects of agonist benzodiazepines (Darragh et al., 1983), although it does exhibit anticonvulsant activity (Scollo-Lavizzari, 1984) and, possibly, an effect on stage 4 sleep (Gaillard and Blois, 1983). Its clinical efficacy as a benzodiazepine antagonist, recently reviewed by Lupolover and Amrein (1984), has been well demonstrated in human volunteers and in patients with benzodiazepine intoxication (Scollo-Lavizzari, 1983). This study was designed to determine dose requirements and the time–intensity profile of response, when anexate was administered in the postoperative period to patients sedated with midazolam.

PATIENTS AND METHODS

Patient selection

Patients selected were caucasian males scheduled for transurethral resection of the prostate (TURP), those excluded being patients already receiving benzodiazepine medication and patients with severe ventilatory disease. The study was approved by the Hospital Ethical Committee and informed consent was obtained from every patient. A total of 70 patients were entered in the trial, but five subjects were subsequently withdrawn and are not included in the results. Of these, two patients departed from the design of the study as a result of a requirement for concurrent opioid-induced pain relief, one antagonist-treated patient died 8 h after surgery because of non-drug related acute valvular heart disease (tricuspid incompetence), one patient was resuscitated from ventricular fibrillation before receiving drug/placebo, and one patient was excluded on the grounds of insufficient data.

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Anaesthesia and recovery

Patients were premedicated with midazolam 7.5 mg by mouth given 30–60 min before operation, supplemented by a further 1–4 mg i.v. if patients were apprehensive before the start of anaesthesia. No hypnotics were given the evening before surgery. Spinal anaesthesia was produced, after crystalloid volume loading, using hyperbaric amethocaine solution 7–14 mg injected via a lumbar space. I.v. increments of midazolam 1–4 mg were given to maintain light to moderate sedation so that patients were drowsy with intermittent or sustained eyelid closure throughout the procedure until their transfer to the recovery ward. On arrival in the recovery ward, vital signs were observed, then patients were scored for degree of sedation, comprehension and collaboration, orientation in time and space, and anterograde amnesia, according to the scoring system given in figures 3, 4, 5 and 6. All scoring was performed by one of three people (D.J.S., R.A.B., A.C.). Anterograde amnesia scores were based on visual recall as follows. A board displaying five pictured items (e.g. animals) was shown to the subject for 1 min. These items were mixed with five similar items on the reverse of the board, which was shown to the subject 5 min later. If no errors were made by the patient in identifying the original five items from the new group of 10, the score was 0. One error scored 1, two errors scored 2 and three errors scored 3, corresponding to scores of slight, moderate and severe anterograde amnesia. For each patient, five different sets of pictures were used, rotated over the seven testing occasions so that the first two boards were used again for the last two testing occasions. Comprehension and collaboration were scored by assessing patients' ability to blow into a hand-held Wright's respirometer. Since vital capacity measured in this way in sedated patients does not truly reflect ventilatory function, the test was used as a means of scoring comprehension and task performance. The ability to complete the test unaided generated a score of 2, completion with assistance scored 1 and failure to complete the manoeuvre even with assistance scored 0. Orientation in time and space were assessed by direct questioning. Correctly stating the month, the days of the week, and date together scored 1, although 2 days either side of the correct date were accepted as correct. A score of 1 was also given when patients correctly identified their location; thus, a fully oriented subject scored 2.

Following these baseline measurements, drug or placebo was given i.v. in a random fashion, administered double-blind from coded ampoules that contained either active drug or a placebo consisting of drug vehicle only. Drug/placebo was given via a large vein in a freely running infusion. Patients 1–31 received anexate in its first formulation (a mixed-micelle solution, 1.0 mg ml^{-1}) and patients 31–65 received the second formulation (aqueous solution 0.1 mg ml^{-1}). In all patients an initial dose of 0.2 mg was given followed by increments of 0.1 mg at 1-min intervals to a maximum of 0.5 mg if the patient had not been restored to normal consciousness by the previous dose. Vital signs, degree of sedation, comprehension, orientation and short-term memory were observed 5 min after the injection of drug or placebo, and at 15, 30, 60, 120 and 240 min.

Statistical analysis was performed using unpaired Student's *t* test on the demographic data and multivariate analysis of variance on the measures of drug efficacy and physiological response.

RESULTS

The drug-treated and placebo groups were the same with regard to number of patients, age, weight, height and ASA class. Both groups required similar doses of amethocaine (subarachnoid) and midazolam i.v. (table I). The midazolam dose range (7.5–55.5 mg) was the total of both preoperative and intraoperative increments of the drug, the individual doses showing marked

TABLE I. *Details of 65 patients undergoing TURP: comparison of control and benzodiazepine antagonist-treated groups. Values are mean ± SD.* $*P < 0.01$

	Placebo group ($n = 33$)	Anexate group ($n = 32$)
Age (yr)	70 ± 13	74 ± 6
Weight (kg)	72 ± 12	70 ± 12
Height (cm)	174 ± 6	170 ± 14
Amethocaine dose (mg) (range 7–14)	9.9 ± 1.5	10.2 ± 1.5
Total midazolam dose (mg) (range 9.5–55.5)	16.3 ± 8.2	16.1 ± 6.1
Anexate/placebo dose (mg) (range 0.15–5)	0.45 ± 0.10*	0.36 ± 0.09*

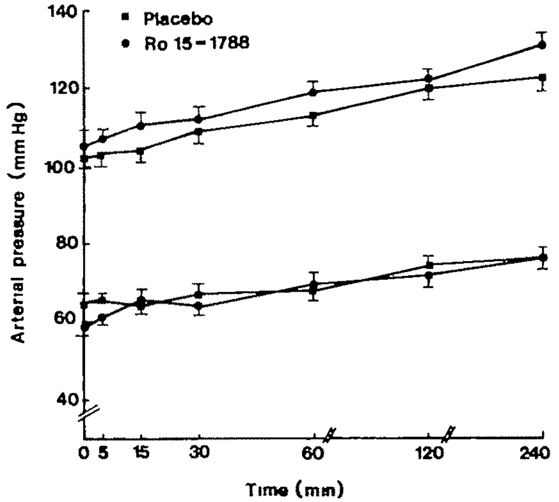

FIG. 1. Systolic and diastolic arterial pressures (mean ± SEM) immediately before anexate/placebo injection (time zero) and for 4 h after injection.

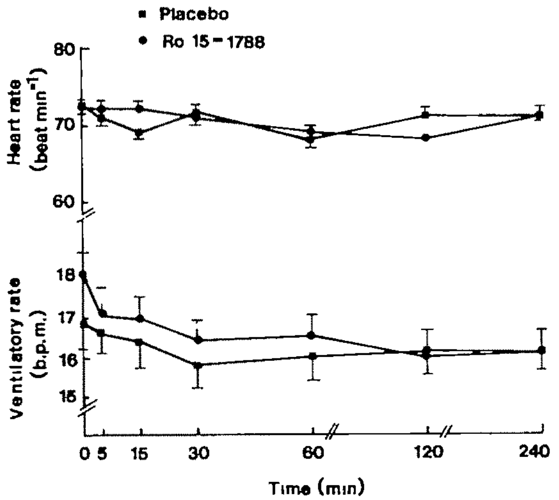

FIG. 2. Heart rate and ventilatory rate (mean ± SEM) immediately before anexate/placebo injection (time zero) and for 4 h after injection.

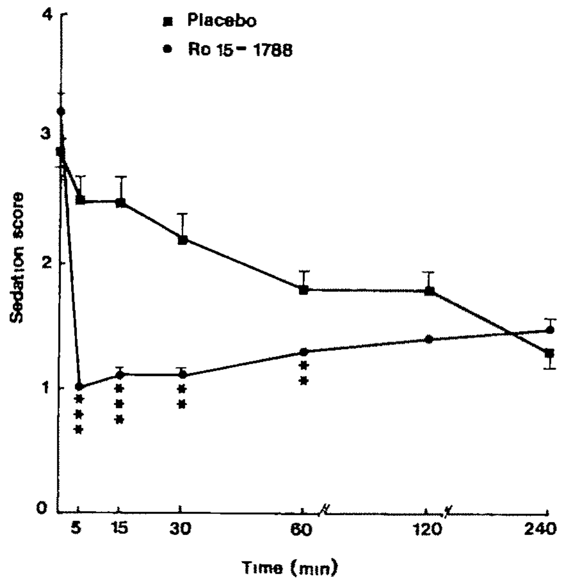

FIG. 3. Sedation scores (mean ± SEM) immediately before anexate/placebo injection (time zero) and for 4 h after injection. Sedation score 0 = awake, tense; 1 = awake, not tense; 2 = drowsy; 3 = sleepy, arousable; 4 = not arousable. $^{**}P < 0.01$; $^{***}P < 0.001$.

variability as a result of considerable variation in the initial dose required to achieve sedation, as well as variation in duration of the operative procedure. Cognitive scores and measurements of vital signs immediately after operation, but before reversal, were the same for each of the two patient groups. The mean "dose" of placebo administered was equivalent to 0.45 ± 0.10 mg of the antagonist (mean ± SD). Mean placebo "dose" significantly exceeded mean anexate dose because of the requirement for the administration of 0.1-mg increments of the blinded drug until normal consciousness was restored.

Vital signs

Differences between the treatment groups were not significant. Mean systolic and diastolic arterial pressures increased progressively after injection in each group as a result of the decreasing effect of the subarachnoid anaesthesia, and although mean systolic arterial pressures in the anexate-treated group were slightly higher than in the control group, the differences were not significant (fig. 1). Mean heart rate remained unchanged after the injection in both groups, and mean ventilatory rates showed slight decreases (1–2 b.p.m.) over the first 4 h after injection which were significant ($P < 0.01$)—ventilatory rates decreasing similarly in both groups (fig. 2).

Reversal of sedation

Dramatic awakening of many previously deeply comatose patients was reflected in the significant immediate reduction in mean sedation scores that

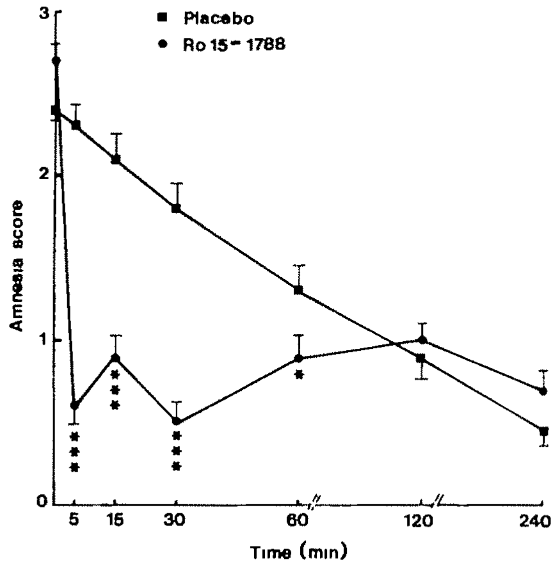

Fig. 4. Anterograde amnesia scores (mean ± SEM) immediately before anexate/placebo injection (time zero) and for 4 h after injection. Amnesia score 0 = no errors on visual recall test; 1 = 1 error (slight amnesia); 2 = 2 errors (moderate amnesia); 3 = 3 or more errors (severe amnesia). $^{***}P < 0.001$; $^{*}P < 0.05$.

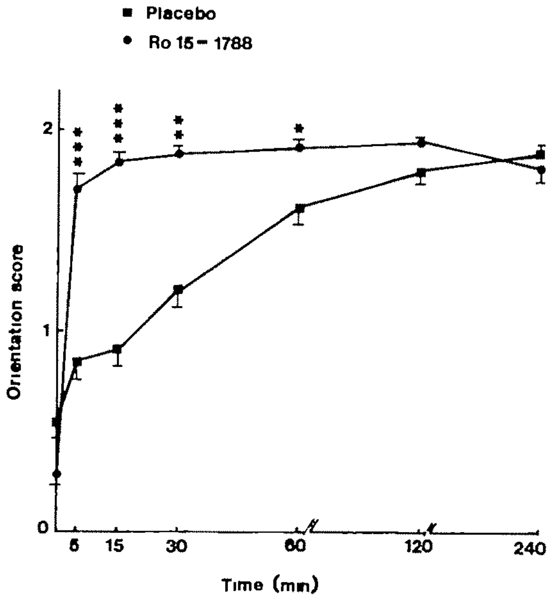

Fig. 5. Orientation scores (mean ± SEM) immediately before anexate/placebo injection (time zero) and for 4 h after injection. Orientation score 0 = total disorientation; 1 = orientated in time or space; 2 = both orientations present. $^{***}P < 0.001$; $^{**}P < 0.01$; $^{*}P < 0.05$.

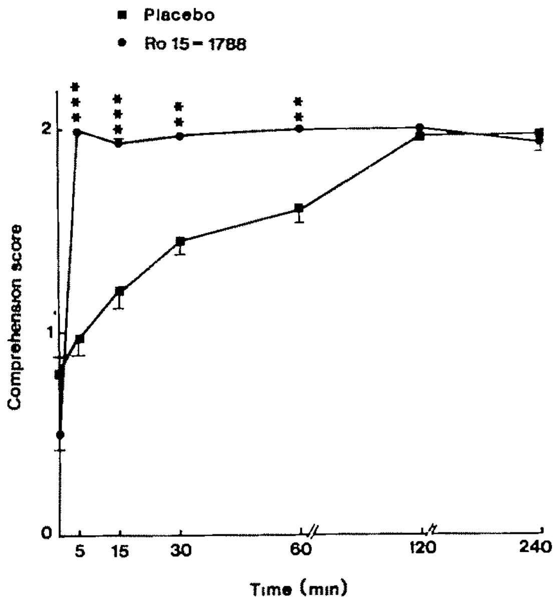

Fig. 6. Comprehension/collaboration scores (mean ± SEM) immediately before anexate/placebo injection (time zero) and for 4 h after injection. Score 0 = no execution of spoken command; 1 = partial execution of command; 2 = execution of command unaided. $^{***}P < 0.001$; $^{**}P < 0.01$.

occurred in the anexate-treated group. This reversal of sedation was apparent by 5 min, without anxiety, and remained significantly better than placebo group scores for 60 min after injection (fig. 3). In the anexate-treated patients a small but statistically significant ($P < 0.005$) increase in mean sedation scores was evident at 4 h when compared with 5 min after injection.

Anterograde amnesia

Severe anterograde amnesia was seen in both treatment groups immediately before injection. The anexate-treated patients showed an immediate improvement 5 min after injection which was maintained throughout the 4-h study period, whereas the placebo group took 2 h to achieve comparable levels of memory retention (fig. 4).

Orientation in time and space

Antagonist-treated patients became almost fully orientated immediately after injection when compared with the poor orientation of the placebo group, an effect that lasted for the remainder of the study. The placebo-treated patients exhibited a gradual improvement in orientation that equalled the drug-treated group by 120 min (fig. 5).

Comprehension and collaboration

Immediately following injection, anexate-treated patients showed marked increases in mean comprehension and collaboration scores that remained significantly greater than the placebo group for 60 min (fig. 6).

Haemoglobin and blood chemistry

Preoperative values for haemoglobin concentration, serum osmalality and the serum concentrations of sodium, potassium, urea, glucose and total protein were within normal limits and there were no differences between the two groups. By the 1st day after operation, all these values had changed but there were no significant differences between the groups in any of these variables.

Local reaction

There appeared to be no pain on injection of drug/placebo, but many subjects were heavily sedated at the time of injection. No venous irritation was observed immediately following the administration of anexate or vehicle in either formulation. At follow-up on the day after surgery, there were two cases of mild phlebitis which were attributed to blood transfusion and the administration of antibiotics i.v.

DISCUSSION

Anexate (Ro 15-1788), as used in this study to reverse sedation by midazolam, appears safe and effective. Changes observed in vital signs were consistent with the decreasing effectiveness of the subarachnoid anaesthesia rather than as consequences of the reversal of the effects of the benzodiazepine, and there was no evidence of immediate or delayed anxiety. Midazolam-induced sedation and impairment of comprehension were restored to normal values 5 min after the injection of anexate, indicating complete reversal of these effects of midazolam, but the less than complete orientation scores of 1.7–1.9, may reflect a residual orientation deficit in some anexate-treated patients or a general failing amongst the older patients in this study. Anterograde amnesia never returned to zero although, as with orientation, the true baseline performance in this test was not established in the preoperative period. Whereas placebo-treated patients tended to become gradually less sedated as a result of the offset of the action of the midazolam, exactly the opposite was true of the antagonist-treated patients who, following reversal, gradually became more sedated because of the offset of the antagonism produced by the anexate. The shorter acting effect of anexate compared with that of midazolam in the doses used is consistent with the difference in elimination half-lives (54–84 min (Klotz et al., 1985)) and 155 min (Lauven et al., 1985) for anexate and midazolam, respectively. The placebo-treated patients also showed spontaneous gradual improvement in orientation, comprehension and anterograde amnesia, again as a result of the offset of the action of the midazolam. However, in contrast to the re-sedation seen in the antagonist-treated group, no deterioration in performance could be demonstrated for the other indices of cognitive function over the 4 h of the study. This difference may be attributable to lack of sensitivity in the other tests of cognition or observer bias, or reflect a differential effect of anexate. Despite the use of a wide dose range of midazolam to achieve moderate sedation (eye closure), all patients had complete reversal of sedation with an antagonist dose of 0.5 mg or less (0.36 ± 0.09 mg (mean ± SD)) when given incrementally over 5 min. The experience of Lauven and colleagues (1985) using much larger i.v. doses in volunteers, produced spontaneous eye-opening in 30 s following 10 mg given to unconscious subjects. Similarly, EEG changes in awake, mildly sedated subjects were abrubtly reversed by 1 min after i.v. anexate 5 mg in a study by Laurian and co-workers (1984). In the elderly men in the present study, the time from the initial injection to eye-opening was often up to 5 min, perhaps as a result of the smaller doses of anexate used, and the probably longer arm–brain circulation times in these patients.

In conclusion, this study found anexate to be safe and effective in doses of 0.5 mg or less in reversing the sedation, disorientation and anterograde amnesia induced with midazolam in a routine clinical setting. As reported in volunteers (O'Boyle et al., 1983; Lauven et al., 1985), our study also showed that mild re-sedation could be seen after 1 h, suggesting that the reversal of long-acting or larger doses of benzodiazepines with anexate may be temporary or incomplete, depending on dose. Further investigation is required to confirm the safety and clinical utility of this drug.

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I.V. TEMAZEPAM: THEORETICAL AND CLINICAL CONSIDERATIONS

N. J. HALLIDAY, J. W. DUNDEE, R. J. T. CARLISLE AND E. McCLEAN

The repeated administration of diazepam to patients in an intensive care environment is associated with the accumulation of an hypnotically active metabolite (Gamble, Dundee and Gray, 1976). The discovery of a sub-population of patients with a prolonged midazolam half-life (Dundee et al., 1986)—although of little clinical importance following a single dose—may result in cumulation of the drug after repeated administrations, or when given by infusion. Thus, there is a clinical need for an injectable benzodiazepine which is intermediate in duration of action between these two and which does not possess any hypnotically active metabolite(s). Temazepam appears to fulfil these criteria: its elimination half-life is 7–10 h (Brittencourt et al., 1979; Fuccella, 1979) and biotransformation is to the inactive glucuronide. Recently, injectable preparations of temazepam were developed by the Department of Pharmacy, The Queen's University of Belfast (McCafferty et al., 1986): one in 90% propylene glycol (PG), the other in 40% sodium salicylate.

We report an evaluation of the use of these in clinical practice. Emphasis was placed on local venous tolerance, on attempts to find the sedative dose in adults, and on a 2-h comparative pharmacokinetic study. A large group of patients received temazepam in the 90% PG preparation, and a smaller volunteer group was given both parenteral preparations, and the commercially available elixir and capsule. All studies were approved by the local medical Ethical Research Committee, and patients and volunteers had given verbal consent to participate.

SUMMARY

Two injectable forms of temazepam, in 90% propylene glycol or 40% salicylic acid, were studied in volunteers, and before surgery in healthy patients. The volunteers also received two forms (capsule and elixir) by mouth. The salicylate preparation was painful on injection and both i.v. formulations caused an unacceptably high incidence of venous thrombosis. Temazepam was detected in plasma earlier following the elixir preparation than the capsule. Plasma concentrations were similar following both injectable preparations. The potency of i.v. temazepam in inducing drowsiness in patients was much less than expected and doses greater than 0.6 mg kg^{-1} were required to produce adequate sedation. There was a significant reduction in thiopentone induction dose in patients receiving temazepam i.v.

PATIENTS, SUBJECTS AND METHODS

Volunteers

Eleven fit, fasting, young, non-smoking students (mean age 22 yr, mean weight 68 kg) took part. They were not on any medication. In random order, each received temazepam 20 mg on four separate occasions either as the elixir (Euhypnos), a capsule (Euhypnos) or an i.v. preparation (two preparations). At least 2 weeks elapsed between administrations.

Injections were made to a large antecubital vein over 20 s. The occurrence of pain on administration was noted, and the vein inspected 14 days later. Arterial pressure (Riva Rocci), heart rate and ventilatory rate were measured at frequent intervals. Blood was drawn from an indwelling i.v. cannula in the contralateral arm at zero, 5, 10, 15, 30, 60, 90 and 120 min, centrifuged and samples stored at −20 °C until they were analysed. Plasma concentrations of temazepam were measured

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using high performance liquid chromatography with ultra-violet detection at 231 nm, based on the method of Ho and co-workers (1983). The within-batch coefficient of variation of a spiked sample of 800 ng ml^{-1} was 3% and the between-batch coefficient of variation of the same sample was 5%.

Patients

All 72 patients were fit, unpremedicated women about to undergo routine gynaecological operations. They received only the PG preparation. An initial study in 10 patients receiving i.v. increments of temazepam 2.5 mg showed that, in doses smaller than 0.5 mg kg^{-1}, sedation was difficult to detect. The remaining patients received at random temazepam 0.5, 0.6, 0.75 or 1 mg kg^{-1} given into a large antecubital vein over 20 s. Discomfort on injection was noted and graded as slight, moderate or severe. Vital signs were recorded as in the volunteer study. The degree of drowsiness was noted at 1-min intervals and graded on a recognized four-point scale ranging from 1 (slight) to 4 (asleep) (Brown and Dundee, 1968).

Ten minutes after the injection of the temazepam, anaesthesia was induced with thiopentone. A standard method of administration of thiopentone was used (Dundee et al., 1982) and the "induction" dose noted. Concurrently, thiopentone requirements were noted in a control group of 39 patients who received no other drugs.

RESULTS

Volunteer study

The vital signs were stable throughout the study in all the volunteers. In the salicylate formulation group 6 complained of pain on injection and two developed a painless thrombosis in the antecubital vein. With the PG 90% preparation five experienced pain, nine developed thrombosis, one of which was painful to touch. None of the 11 volunteers receiving temazepam 20 mg i.v. developed more than slight drowsiness over the 2-h period of the study although both oral preparations produced a moderate degree of sedation in seven or eight subjects.

The mean plasma concentrations of temazepam, following the four administrations, are shown in figure 1, from which the SD is omitted for the sake of clarity, especially as it is of no significance. The drug was detected earlier with the elixir than with the capsule preparation, and average plasma concentrations were significantly greater with the former at 15 and 30 min ($P < 0.02$). Plasma concentrations appeared to be still increasing at 2 h, at which time there was no difference between the concentrations attained with the two oral preparations. There was no significant difference in mean temazepam concentrations with either i.v. preparation at any time during the study. By 2 h the mean concentrations achieved after temazepam 20 mg were similar in all four studies.

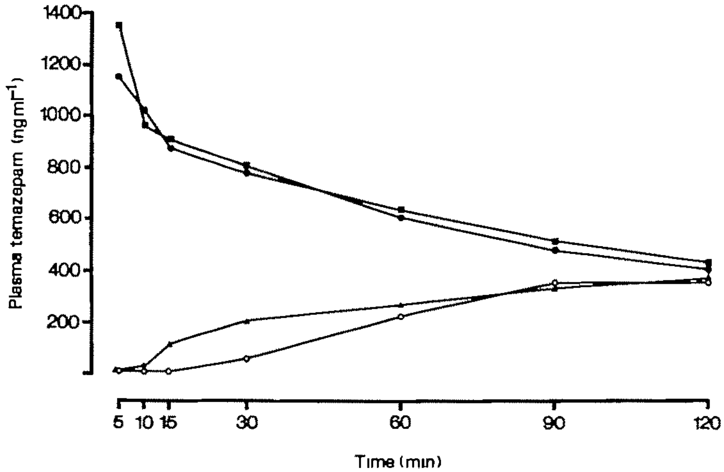

FIG. 1. Mean plasma concentations following temazepam 20 mg by mouth either as Euhypnos elixir (▲) or Euhypnos capsule (○), or i.v. formulated in 90% propylene glycol (●) or 40% sodium salicylate (■).

Patient study

Table I shows that the mean ages and weights were comparable in all four dosage groups. With all doses, sedation was maximal at 3 min following injection. Figure 2 shows the level of sedation attained at this time in each group. The response to i.v. temazepam was variable with doses less than 0.6 mg kg^{-1}. Adequate sedation (eyes closed but easily rousable), was achieved 3 min after injection in 15/31 patients receiving temazepam 0.5 or 0.6 mg kg^{-1}. There was a significant increase in adequate sedation to 26/31 in those receiving the higher (0.75–1.0-mg kg^{-1}) doses ($P = 0.007$). Only four of the 16 patients receiving the maximal dose, 1 mg kg^{-1}, showed marked sedation and required no thiopentone to induce anaesthesia.

TABLE I. *Ages and weights (mean ± SEM) of patients receiving i.v. temazepam 0.5, 0.6, 0.75 or 1.0 mg* kg^{-1}

Dose (mg kg^{-1})	*n*	Age (yr)	Weight (kg)
0.5	15	31 ± 1.8	60 ± 2.7
0.6	16	33 ± 2.6	60 ± 3.7
0.75	15	34 ± 2.3	61 ± 2.8
1.0	16	31 ± 1.7	57 ± 2.8

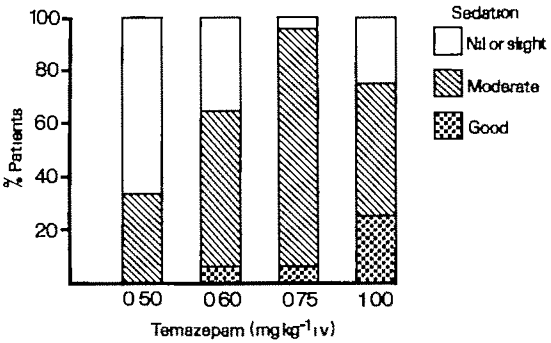

FIG. 2. Sedation scores at 3 min, following i.v temazepam in the four doses.

With doses of 0.5–1.0 mg kg^{-1}, pain on injection occurred in 60% patients, being moderate to severe in 36%.

Thiopentone requirements were significantly lower ($P < 0.001$) in those patients who received i.v. temazepam than in the control group (no temazepam) with mean values of 2.4 ± 0.16 (SEM) mg kg^{-1} and 4.6 ± 0.18 (SEM) mg kg^{-1}, respectively.

DISCUSSION

Circumstances limited the period of observation in our volunteers to 2 h and in the light of the findings it was decided not to continue with a more extensive evaluation. We have previously found that a 20-mg tablet is suitable for night sedation or preanaesthetic medication (Wilson et al., 1986); this study shows that a similar dose given i.v. produced a lesser effect. A possible explanation may be an altered initial distribution of the drug following i.v. administration, with a greater proportion being distributed to tissues outside the central nervous system. The two oral preparations behave similarly except for the slightly earlier onset of action with the less palatable elixir.

With both i.v. preparations of temazepam there was an unacceptably high incidence of pain on injection with some degree of discomfort associated with more than 50% of the administrations of these formulations. Despite the theoretical advantages of this injectable benzodiazepine, venous intolerance precludes further clinical use of either formulation.

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NEOSTIGMINE IN THE ANTAGONISM OF THE ACTION OF ATRACURIUM

M. A. FOX, S. J. KEENS AND J. E. UTTING

SUMMARY

Antagonism of atracurium-induced neuromuscular blockade with neostigmine (one or two doses of 2.5 mg) was compared, using electromyography, with spontaneous recovery. Two levels of blockade were studied, one in which the initial response of the train-of-four has reached 10% of control and the other 50% of control. Adequate recovery was considered to be present when the ratio of the fourth response to the first (train-of-four ratio) had reached 70%. Neostigmine always accelerated recovery and "neostigmine block" was not detected. This acceleration of recovery after neostigmine was most marked with the greater degree of blockade, but two doses of neostigmine were no more effective than one. Spontaneous recovery to the train-of-four ratio of 70% was slow, in the order of 1 h after an initial dose of 0.5 mg kg^{-1} and 45 min after incremental doses of 0.2 mg kg^{-1}. It is concluded that antagonism of atracurium with one dose of neostigmine is usually desirable, that two doses are unnecessary, and that spontaneous recovery is slower than is generally realized.

Early clinical investigators of atracurium were impressed by the rapid spontaneous recovery of neuromuscular function and, from their observations, anticipated that the antagonism of atracurium-induced neuromuscular blockade (with an anticholinesterase) might not always be necessary (Payne and Hughes, 1981). It has been suggested that adequate clinical recovery takes place within 30 min or so, and there is a view amongst anaesthetists that blockade produced by atracurium does not usually require the use of an antagonist—although the proviso is usually made that the return of adequate neuromuscular transmission must be demonstrated with the appropriate monitoring equipment. As with pancuronium and tubocurarine, however, there is considerable individual variation in the rate of recovery from any given degree of atracurium-induced neuromuscular blockade (Katz et al., 1982). It has been suggested that, if adequate spontaneous recovery has not occurred at the end of surgery and the administration of an anticholinesterase is thought to be necessary, the dose requirements for, and the rates of recovery after, neostigmine are similar to those of metocurine (Basta et al., 1982).

Thus despite the ease with which atracurium-induced blockade can be reversed (Basta et al., 1982; Rowlands, 1983; Eager, Flynn and Hughes, 1984), there are reports of difficulty in antagonizing its action (Duncan, 1983; Biazzari-Schmid and Desai, 1986). On the other hand, allowing spontaneous recovery, or using only very small doses of neostigmine, has been advocated because of fears of inducing blockade with neostigmine. This block has been demonstrated after antagonizing the action of tubocurarine, dimethyl tubocurarine and gallamine with two doses of neostigmine, each of 2.5 mg, separated by 2 min (Payne, Hughes and Al Azawi, 1980). This regimen sometimes resulted in an increase in tetanic fade (50 Hz) with an apparent difference in severity between the different drugs. The one report of the use of two doses of neostigmine to reverse blockade by atracurium, however, failed

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to show any overt untoward effects (Eager, Flynn and Hughes, 1984).

There is little or no firm guidance in the literature as to the appropriate dose of neostigmine for a given degree of neuromuscular blockade or, indeed, as to whether the fears of inducing neostigmine-induced blockade are justified when using conventional doses of neostigmine to antagonize the action of atracurium. We have, therefore, undertaken a study using electromyographic monitoring in an attempt to clarify the situation. Fixed doses of neostigmine were used as this is a more usual clinical practice than using a weight-related dose.

PATIENTS AND METHODS

Forty patients presenting for general or gynaecological surgery were investigated. Informed consent was obtained, and the study was approved by the appropriate ethics committee. All patients were graded as ASA I or II and were free from neurological disease. They presented for a wide range of general surgical and gynaecological procedures including herniorraphy, cholecystectomy, hysterectomy, mastectomy and laparoscopy.

Premedication was with either promethazine by mouth the night before surgery or a mixture of morphine and cyclizine (Cyclimorph) i.m. Anaesthesia was induced with fentanyl, droperidol and thiopentone, and maintained with 70% nitrous oxide in oxygen, with assisted ventilation as required while control measurements (at least 10 satisfactory responses to the supramaximal train-of-four stimuli) were obtained with the electromyograph. Atracurium 0.5 mg kg^{-1} was then administered. Controlled ventilation was continued with nitrous oxide in oxygen with no added volatile agent and a tracheal tube was inserted about 2 min after the atracurium had been given. Ventilation was adjusted to maintain an end-tidal carbon dioxide tension of 4.75–5.25 kPa. Increments of atracurium 0.2 mg kg^{-1} were given when the first electromyographic response of a train-of-four (A') had recovered to 10% of the control value (A). Increments of fentanyl were given as clinically indicated. Atropine 1.2 mg was given with the initial dose of neostigmine and a further dose of atropine 0.6 mg given if a second dose of neostigmine was administered.

Neuromuscular function was assessed using a Medelec MS6 recorder. A train-of-four (TOF) sequence of supramaximal stimuli (0.2 ms, 2 Hz) at 12-s intervals was applied to the ulnar nerve. The resulting electromyographic compound action potential was recorded from surface electrodes over the adductor pollicis muscle and recorded on light sensitive paper.

The study was designed to compare recovery, with and without neostigmine, from two levels of atracurium-induced neuromuscular blockade. The degree of blockade was assessed by determining the ratio of the first electromyographic response of the train-of-four to the response to the train-of-four before the administration of atracurium (A'/A). In the more complete degree of blockade studied the A'/A ratio was approximately 10% and in the lesser degree of blockade the A'/A ratio was approximately 50%. The initial degree of blockade is characterized by the variable, A'/A alone, because D' was too small to measure accurately when A'/A was 10% and the ratio D'/A', the train-of-four (TOF) ratio, could not be determined. (Its inclusion when considering the lesser degree of block (A'/A = 50%) adds confusion to the interpretation of the results.) In recovery, however, both the ratio A'/A and the ratio of the fourth electromyographic response in the train of four to the first were studied (D'/A'; the train-of-four ratio).

Ten patients were allowed to recover spontaneously; 20 patients received neostigmine 2.5 mg, one group of 10 when A'/A was 10% and the other 10 when it was 50%; in addition two groups of five patients each received two doses of neostigmine 2.5 mg (the second dose 2 min after the first), one when the A'/A was 10% and the other when it was 50%.

The times measured were the times until A'/A and D'/A' had attained 70% (the latter taking longer than the former). Zero times for the group which recovered spontaneously were taken as being when A'/A was exactly 10% and 50%. When neostigmine 2.5 mg was given at either of the two degrees of blockade, zero time was taken as the point at which the neostigmine was actually administered; when two doses of neostigmine were given, zero time was taken as the time at which the first dose was administered.

Neuromuscular monitoring was continued for at least 10 min after the reversal of blockade from an A'/A ratio of 50% and for at least 20 min after the reversal of blockade from an A'/A ratio of 10% or until the TOF ratio (D'/A') had recovered to more than 75%.

TABLE I. *Mean age and weight (SD) of the groups of patients studied together with the numbers and the male/female (M/F) ratio. The initial block is measured by the ratio A′/A. The dose of neostigmine is indicated; in the group given 5.0 mg the dose was divided; in the spontaneous group no neostigmine was given*

	Initial block	No.	Age (yr)	Weight (kg)	M/F
Spontaneous	10+50%	10	55.0 (14)	72.0 (11.8)	4:6
Neostigmine 2.5 mg	10%	10	43.5 (14)	73.9 (14)	5:4
	50%	10	47 (12)	63.9 (13)	3:7
Neostigmine 5.0 mg	10%	5	53 (7)	66.5 (9.1)	2:3
	50%	5	43 (8)	64.2 (4.7)	5:0

TABLE II. *Recovery time (min (SD)) to 70% of ratios A′/A and D′/A′ for the two degrees of block studied (when A′/A initially was 50% and 10%). Spontaneous recovery is compared with the use of neostigmine (Neo.) in one and two doses. Statistical comparisons are with spontaneous recovery* (**P < *0.01;* ***P < *0.001*). n = *Number of patients in each group*

		Time to 70% recovery of ratio (min)		
Initial block (A′/A)	Ratio	Spontaneous (*n* = 10)	Neo. 2.5 mg (*n* = 10)	Neo 2.5+2.5 mg (*n* = 5)
50%	A′/A	7.3	2.8***	2.2**
		(2.7)	(0.6)	(0.8)
	D′/A′	14.3	3.5***	3.0**
		(6.2)	(1.2)	(1.0)
10%	A′/A	25.0	8.2***	7.4**
		(9.5)	(2.9)	(1.7)
	D′/A′	32.3	12.0***	11.2**
		(10.4)	(3.5)	(2.3)

The significance of any differences in the mean recovery times was assessed using Student's unpaired *t* test.

RESULTS

The distribution of age, weight and sex is given in table I and the results are summarized in table II.

Recovery from neuromuscular blockade was always more rapid after the administration of neostigmine than during spontaneous recovery. The time to 70% spontaneous recovery of the initial twitch (A′/A) and the TOF ratio (D′/A′) from the time A′/A was 50% was significantly longer ($P < 0.001$) than for the same recovery to occur after the administration of neostigmine 2.5 mg. The time to 70% spontaneous recovery from blockade in which A′/A was 10% for A′/A and D′/A′ was also significantly longer ($P < 0.001$) than the time taken to achieve the same level of recovery, after neostigmine 2.5 mg had been given.

There were significant differences in the times of recovery ($P < 0.01$ for both A′/A and D′/A′) after two doses of neostigmine compared with spontaneous recovery (there were only five patients in this last group). However, although two doses of neostigmine resulted in a marginally quicker recovery than a single dose, this failed to achieve statistical significance. The second dose of neostigmine always caused an increase in the rate of recovery of both A′/A and D′/A′; there was never any decrease in the ratios after two doses of neostigmine had been given.

The time taken for D′/A′ to return spontaneously to 70% after an intubation dose of atracurium 0.5 mg kg^{-1} was 65.5 min with a standard deviation of 11.9 min; this compares with 45.8 min (±11.8 min) to achieve the same degree of recovery after the last of a series of incremental doses of 0.2 mg kg^{-1} had been given. All patients were shown to have full clinical recovery of neuromuscular function at the end of the study.

DISCUSSION

A TOF ratio of 70% is often considered to represent the point at which recovery can be considered adequate and safe (Brand et al., 1977), although it should be added that some workers suggest that a TOF ratio of 50% is adequate for spontaneous recovery from atracurium (Jones, Pearce and Williams, 1984). It has been shown that, during recovery from a tubocurarine-induced neuromuscular blockade, changes in ventilatory muscle function of clinical significance can be demonstrated unless the TOF ratio is greater than 60% (Ali, Wilson and Kitz, 1975). It is generally agreed that a train-of-four response is a more sensitive indicator of fade than tetanic stimulation at 50 Hz for 1 s (Hughes and Payne, 1983) or for 5 s (Ali et al., 1981). For these reasons we chose to monitor neuromuscular function using a train-of-four technique, and followed recovery until a TOF ratio of at least 70% had been achieved. Not surprisingly, neostigmine always increased the rate of recovery as compared with the rate of spontaneous recovery. Although a second dose of neostigmine appeared to result in marginally faster rates of recovery this was neither practically nor statistically significant.

It has been demonstrated (Payne, Hughes and Al Azawi, 1980) that, when a second dose of neostigmine 2.5 mg was given 2–5 min after the first dose (in an attempt to reverse the effects of gallamine or dimethyl tubocurarine), there was an increase in tetanic fade of frequency 50 Hz and duration 1 s. This was most marked when the patient was receiving 2% halothane as an adjuvant. Although we gave two doses of neostigmine separated by a 2-min interval, none of our patients showed any increase in fade in the train-of-four. Every patient appeared to show an increase in the rate of recovery of both A′/A and D′/A′. Thus using the train-of-four, we have been unable to demonstrate any adverse neuromuscular effect when two doses of neostigmine were given to antagonize atracurium-induced neuromuscular blockade. However, had halothane been used as an adjuvant or tetanus as a method of monitoring, or both, fade might have been demonstrated.

Neostigmine in a dose of 2.5 mg proved effective in reversing both greater and lesser degrees of blockade to a TOF ratio of 70% in the clinically acceptable times of 12.0 and 3.5 min, respectively; this compares with the slower spontaneous recovery times of 32 and 14 min. In common with previous reports (Katz et al., 1982) we found a wide scatter in the rates of spontaneous recovery, one patient taking as long as 49 min to recover a TOF ratio of 70% from the time A′/A was 10%.

An A′/A ratio of 10% does not indicate a very great degree of neuromuscular blockade; from the clinical point of view it is approximately the level at which a patient may start to swallow on a tracheal tube or move in response to surgical stimulation.

The time to maximal effect of atracurium is 7–8 min (Ramsey et al., 1982; Pearce, Williams and Jones, 1984). If 8 min is subtracted from the measured recovery times (results) it can be seen that spontaneous recovery after a single intubation dose of atracurium 0.5 mg kg^{-1} takes about 1 h, whereas recovery after a series of increments of 0.2 mg kg^{-1} occurs in approximately 38 min. The suggestion that recovery from full blockade without the use of neostigmine occurs in about 35 min (Walker, 1985), would seem to apply only if increments have been given and possibly, as in this study, when no volatile supplements have been used.

Ideally, neuromuscular function should be assessed by either mechanical or electromyographic techniques. Whilst this is to be expected when studying neuromuscular function, it is not necessarily appropriate or practical in clinical practice when it is more normal to measure the intensity of neuromuscular blockade by tactile or visual assessment of the TOF. Counting the number of twitches present in the TOF or post-tetanic twitches is straightforward and a good guide in determining the need for incremental doses of neuromuscular blocker. However, during recovery, when all four twitches of a TOF are present, measuring the degree of blockade depends on assessing fade. It has been shown that even very experienced observers cannot reliably distinguish the amount of fade in the TOF ratio 40–70% (Viby-Mogenson et al., 1985). Therefore, in the absence of sophisticated monitoring of neuromuscular function if would seem prudent to antagonize the action of atracurium unless there is a specific contraindication to the use of antagonizing agent. There seems to be little difference in the rate of recovery whether neostigmine 2.5 or 5.0 mg is used. In the absence of a volatile agent there is little risk of inducing a neostigmine block when antagonizing atracurium.

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ANTAGONISM OF VERCURONIUM-INDUCED NEUROMUSCULAR BLOCKADE WITH EDROPHONIUM OR NEOSTIGMINE

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SUMMARY

Antagonism of vecuronium-induced neuromuscular blockade was attempted, at varying degrees of spontaneous recovery, with edrophonium 0.5 mg kg^{-1} or neostigmine 0.05 mg kg^{-1} in two groups of 20 patients. Neuromuscular blockade was monitored using a train-of-four (TOF) stimulation. Adequate antagonism of neuromuscular blockade, defined as a sustained TOF ratio of 0.7 or more, was attained in all 20 patients given neostigmine and in 13 out of 20 given edrophonium. Five of the remaining seven patients given edrophonium had shown three or less responses to TOF stimulation before antagonism. While the time to onset of the action of edrophonium (22 s) was not significantly shorter than neostigmine (26 s), the time taken to attain a TOF ratio of 0.7 was significantly shorter with edrophonium (67 s compared with 194 s with neostigmine). It is concluded that edrophonium 0.5 mg kg^{-1} does not consistently antagonize vecuronium-induced neuromuscular blockade, particularly if there are three or less responses to a TOF stimulation present before antagonism.

Edrophonium has recently been recommended as the antagonist of choice with which to antagonize non-depolarizing blockade (Bevan, 1979; Baird, Bowman and Kerr, 1982; Cronnelly and Morris, 1982; Cronnelly, Morris and Miller, 1982; Baird and Kerr, 1983; Jones, Pearce and Williams, 1984). Its main advantages are a rapid onset of action and minimal muscarinic side-effects (Cronnelly, Morris and Miller, 1982; Mirakhur, 1985). In most of these studies, neuromuscular blockade was antagonized at a standard and appreciable degree of recovery from blockade—a situation not always prevalent in routine anaesthetic practice.

Antagonism of relatively more profound degrees of blockade may be difficult with edrophonim (Kopman, 1979; Lavery, Mirakhur and Gibson, 1985). In the present study we have assessed the effectiveness of edrophonium 0.5 mg kg^{-1} in the antagonism of vecuronium-induced neuromuscular blockade at varying degrees of recovery. A group given neostigmine 0.05 mg kg^{-1} was included for comparison.

PATIENTS AND METHODS

Following approval from the Regional Ethical Committee, 40 patients (ASA grade I) scheduled for elective surgery requiring neuromuscular blockade were included after their informed consent had been obtained.

Patients were premedicated with diazepam 10 mg orally about 1 h before operation. Anaesthesia was induced with thiopentone and maintained with nitrous oxide and 0.5–1.0% enflurane in oxygen, plus fentanyl 2–3 μg kg^{-1}. Ventilation was adjusted to maintain normocarbia (end-tidal carbon dioxide concentrations of 4.5–5.0%). Neuromuscular transmission was monitored by applying supramaximal square wave stimuli of 0.2 ms duration to the ulnar nerve at the wrist in a train-of-four sequence (TOF) at 2 Hz every 10 s. The contractions of the adductor pollicis were recorded using a neuromuscular function analyser (Myograph 2000, Biometer Limited). Vecuronium was given in an initial dose of 0.1 mg kg^{-1}, further increments of 0.025–

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0.05 mg kg^{-1} being administered at the recovery of all four responses to TOF stimulation.

Enflurane was discontinued at the end of surgery when antagonism of blockade was attempted irrespective of the degree of block present — provided that at least one response was evoked by TOF stimulation. Twenty patients each were randomly allocated to receive edrophonium 0.5 mg kg^{-1} or neostigmine 0.05 mg kg^{-1}, in a mixture with atropine or glycopyrrolate. The subsequent recovery of neuromuscular transmission was recorded for at least 10 min in all patients. A TOF ratio of 0.7 or more was considered to indicate adequate antagonism (Ali and Savarese, 1976; Ali et al., 1981). If adequate antagonism was not attained in 10 min, a further dose (or doses), of the anticholinesterase, equivalent to half the initial dose, was given. Adequacy of antagonism was assessed for at least the next 30 min in the recovery ward using recognized clinical criteria such as the ability to breathe deeply, cough and maintain a sustained head lift.

The height of the first twitch (T1) in the TOF sequence as a percentage of control value obtained before the administration of the neuromuscular blocker, and the TOF ratio (ratio between the fourth and first twitches in the same TOF sequence), were measured before the administration of the anticholinesterase. The highest sustained values for these measurements were again recorded after the administration of the antagonist. In addition, the time to the onset of a measurable effect, the time taken to attain a TOF ratio of 0.7 and the TOF ratios at 50, 75 and 100% recovery of T1 were measured. The groups were compared using a Student's *t* test, non-parametric data being analysed using a Chi-square test with Yates' correction.

RESULTS

There were no significant differences in the ages and weights in the groups, or in the degree of neuromuscular blockade present before the administration of the relevant anticholinesterase agent (table I). Seven patients in the edrophonium group and eight in the neostigmine group showed three or less responses to TOF stimulation before antagonism. In these patients the average heights of T1 were 22 and 16% of control, respectively (ns).

A representative TOF recording is shown in figure 1. It is clear that adequate antagonism (TOF ratio of 0.7) was achieved more rapidly following edrophonium than following neostigmine. However, figure 1 also shows that when antagonism was attempted at more profound degrees of neuromuscular blockade, adequate antagonism was not attained even though the edrophonium started to act rapidly.

TABLE I. *Physical characteristics and degree of blockade present before antagonism (mean values ± SEM (range))*

	Edrophonium	Neostigmine
Age (yr)	34 ± 3.7	42 ± 4.5
Weight (kg)	71 ± 3.4	69 ± 3.2
T1 before antagonism (%)	38 ± 3.7 (8–76)	33 ± 4.2 (8–76)
TOF ratio before antagonism	0.17 ± 0.035 (0.04–0.50)	0.19 ± 0.031 (0.06–0.04)
Number showing three or fewer twitches before antagonism	7	8

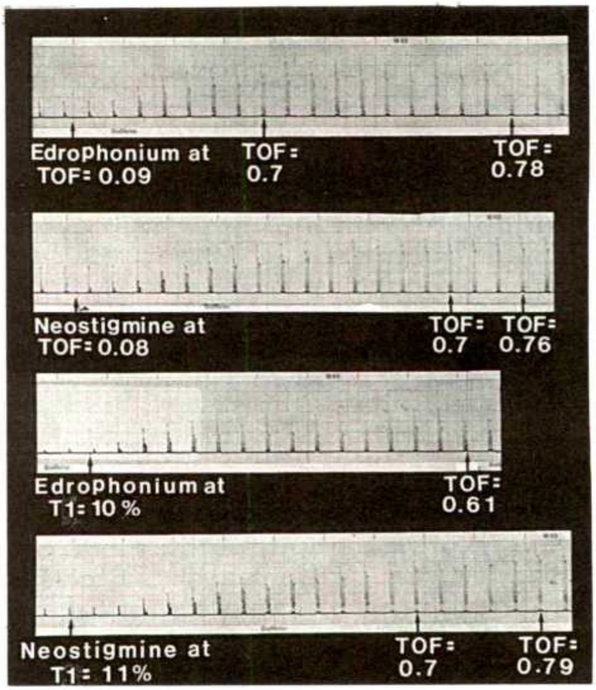

FIG. 1. Representative TOF recordings from four patients during antagonism of vecuronium-induced block. The top two recordings refer to patients in whom blockade was antagonized at TOF ratios of 0.09 and 0.08, respectively. Blockade was adequately antagonized in both, but more rapidly following edrophonium. In the two lower traces antagonism was attempted at relatively deeper degrees of block (no TOF responses). It is clear that neostigmine did antagonize the block adequately, whereas edrophonium failed to do so (TOF 0.61).

The average onset times and the times taken to attain TOF ratios of 0.7 in the two groups are given in table II. There was no significant difference in the time to onset of effect (22 s for edrophonium, 26 s for neostigmine), but the time taken to attain a sustained TOF ratio of 0.7 was significantly less ($P < 0.05$) with edrophonium (67 s) in comparison with neostigmine (194 s). However, seven patients given edrophonium failed to attain a TOF ratio of 0.7 (table II) and, hence, the time to TOF ratio of 0.7 refers to only 13 patients in this group. The individual peak TOF ratios attained with the two anticholinesterase agents are shown in figure 2. These varied from 0.7 to 1.0 with a mean of 0.85±0.022 (SEM) in the neostigmine group, and from 0.53 to 0.96 with a mean value of 0.74±0.028 (SEM) in the edrophonium group (E_{20} in figure 2). This difference in the average peak TOF ratios between the groups was significant ($P < 0.01$). However, if the seven patients in the edrophonium group who did not attain a TOF ratio of 0.7 are excluded, the average peak TOF in the remaining 13 patients (E_{13} in figure 2) in this group was 0.82±0.021 (SEM), which was not significantly different from that in the neostigmine group.

TABLE II. *Times to onset of action and to the attainment of a TOF ratio of 0.7 (mean values ± SEM). *Significant differences between the groups: *P < 0.05 (Student's t test), †P < 0.025 (χ^2 with Yates' correction). ‡Refers to only 13 patients in the edrophonium group (see text)*

	Edrophonium	Neostigmine
Time to onset of effect (s)	22±1.9	26±2.4
Time to TOF ratio of 0.7 (s)‡	67±8.3*	194±45.6*
Number failing to attain TOF ratio of 0.7	7†	0†

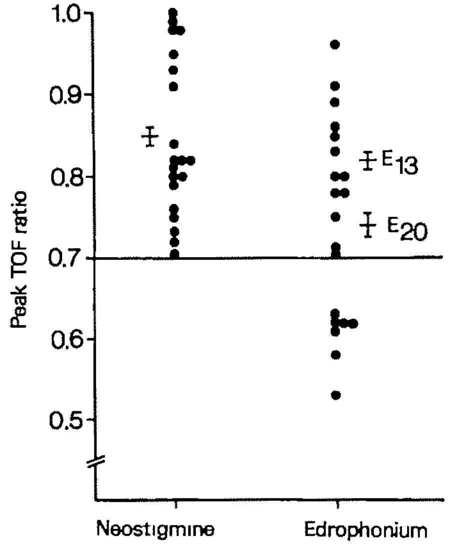

FIG. 2. Peak TOF ratios in individual patients after the administration of the anticholinesterase agents. Horizontal line and bars represent mean ± SEM values. E_{20} refers to average peak TOF ratio in all 20 patients in the edrophonium group and E_{13} refers to peak TOF ratio in the 13 patients in this group who attained a TOF ratio of 0.7 or more (adequate antagonism).

TABLE III. *TOF ratios at 50, 75 and 100% recovery of T1 (first twitch in the TOF sequence) (mean values ± SEM). *Significant difference (P < 0.05) between edrophonium and neostigmine*

	TOF ratio		
	Edrophonium		Neostigmine
Height of T1 (%)			
50	0.34±0.026	*	0.26±0.029
75	0.56±0.032	*	0.47±0.029
100	0.70±0.026		0.67±0.031

Five of the seven patients who failed to attain a TOF ratio of 0.7 with edrophonium showed three or less responses to TOF stimulation before the administration of the antagonist. The two remaining patients in whom antagonism was inadequate with edrophonium had TOF ratios of 0.11 and 0.18 before antagonism.

Adequate antagonism in all these patients was attained following a further period of ventilation and the administration of one or two further doses of edrophonium. In contrast, in all patients given neostigmine, including the eight who did not show all four responses to TOF stimulation before antagonism, blockade was reversed adequately.

The TOF ratios at 50, 75 and 100% T1 twitch height in patients in the two groups are shown in table III. The TOF ratios during antagonism are higher after edrophonium, being significantly so at 50 and 75% heights of T1 ($P < 0.05$).

DISCUSSION

The present study confirms that, when considered overall, edrophonium, in a dose of 0.5 mg kg^{-1} as used in the present study and recommended by Cronnelly, Morris and Miller (1982) and Jones, Pearce and Williams (1984), antagonized vecuronium-induced blockade significantly more rapidly than neostigmine. However, neuromuscular blockade could not be *adequately* antagonized (as defined by a TOF ratio of 0.7) in seven out of 20 patients (35%) given this dose of edrophonium, the majority of these (five out of seven) showing three or less responses to a TOF stimulation before antagonism. A previously published study (Baird, Bowman and Kerr, 1982) suggested that edrophonium in doses of 0.5–1.0 mg kg^{-1} would be the reversal agent of choice with which to antagonize a vecuronium-induced blockade compared with blockade produced by pancuronium or tubocurarine. We are unable to substantiate this for the 0.5-mg kg^{-1} dose — particularly in patients with relatively more marked degrees of blockade: in 35% of patients blockade could not be adequately antagonized. Perhaps Baird and his co-workers (1982) based their assertions on the basis of their work in cats. They studied only a total of nine patients who received edrophonium in doses ranging from 0.1 to 1 mg kg^{-1} and in whom twitch heights had recovered to at least 25% of control. Other workers have also reported difficulty in antagonizing relatively profound neuromuscular blockade produced by vecuronium, pancuronium or atracurium adequately with doses of edrophonium similar to that used in the present study—particularly if three or fewer responses to a TOF stimulation were present (Kopman, 1979; Foldes et al., 1981; Rupp, McChristian and Miller, 1984; Lavery, Mirakhur and Gibson, 1985). In the present study, blockade in two patients was not antagonized, despite considerable recovery (as shown by TOF ratios of 0.11 and 0.18, respectively) before antagonism. Neostigmine, on the other hand, antagonized neuromuscular blockade adequately in all 20 patients in the present study, including those not showing all four responses to TOF stimulation.

It is possible that a larger initial dose of edrophonium may have been successful in antagonizing relatively more profound blockade, since the administration of one or two additional doses (of edrophonium) produced adequate antagonism in these patients. However, with a neuromuscular blocking agent such as vecuronium, which has a short recovery index, it is likely that further spontaneous recovery of blockade was taking place in the intervening period of more than 10 min. Moreover, other workers using edrophonium, even in larger doses than those used in the present study, have failed to show adequate antagonism of relatively deeper blockade induced by vecuronium — or atracurium, an agent not dissimilar to vecuronium in its recovery characteristics (Hughes, Astley and Payne, 1984; Engbaek et al., 1985). In addition, it has been shown that larger doses of edrophonium would exert greater muscarinic effects and require larger doses of atropine, thus losing one of the major benefits of the use of edrophonium (Engbaek et al., 1985).

The potency ratio between edrophonium and neostigmine has been given as 11.6:1 by Cronnelly, Morris and Miller (1982), and as 16:1 by Breen and his colleagues (1985) using different methods of estimation. The ratio of 10:1 used in the present study is closer to that given by Cronnelly and his colleagues (1982). The present study was, however, not comparing strictly equipotent doses, but looking at the efficacy of commonly advocated doses of the two anticholinesterase drugs.

Presence of higher TOF ratios and, consequently, less fade with edrophonium at similar heights of T1 probably reflects its greater presynaptic activity and has previously been reported during antagonism of pancuronium and atracurium-induced blockade (Donati, Ferguson and Bevan, 1983; Jones, Pearce and Williams, 1984; Lavery, Mirakhur and Gibson, 1985). However, this does not appear to be of any beneficial value in relatively more profound vecuronium-induced blockade.

In conclusion, edrophonium in a dose of 0.5 mg kg^{-1} does not adequately and reliably antagonize vecuronium-induced neuromuscular blockade—particularly where three or less responses to a TOF stimulation are present before antagonism. Neostigmine 0.05 mg kg^{-1} provides better and more reliable antagonism in such situations.

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ANTAGONISM OF VECURONIUM AND ATRACURIUM: COMPARISON OF NEOSTIGMINE AND EDROPHONIUM ADMINISTERED AT 5% TWITCH HEIGHT RECOVERY

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SUMMARY

In 39 healthy patients antagonism, by neostigmine 0.07 mg kg^{-1} or edrophonium 0.8 mg kg^{-1}, of neuromuscular blockade induced by vecuronium or atracurium, was compared. Reversal was attempted when the height of the single twitch (TH) had recovered spontaneously to 5% of the control value. The evoked responses, initially single twitch, then train-of-four (TOF) were observed until the TOF ratio was 70%. Induced recovery from TH 5% to 25% was shorter following edrophonium than following neostigmine with both vecuronium ($P < 0.05$) and atracurium ($P < 0.05$). The recovery indices and times until TH was 75% of control and until the TOF ratio was 70% were not different. The time from a TH of 75% to a TOF ratio of 70% was shorter following neostigmine than following edrophonium with both vecuronium ($P < 0.01$) and atracurium ($P < 0.01$). Edrophonium had a much more variable effect on vecuronium than on atracurium. These results show that although the onset of action of edrophonium was faster than that of neostigmine, this did not lead to a faster clinical recovery, and antagonism by edrophonium may be delayed in a number of patients if vecuronium is the neuromuscular blocker.

It has been shown that edrophonium can rapidly and reliably antagonize neuromuscular blockade induced by vecuronium (Foldes et al., 1981; Baird, Bowman and Kerr, 1982) and atracurium (Baird and Kerr, 1983; Jones, Pearce and Williams, 1984). In all these studies, spontaneous recovery had occurred to the extent that there were four responses to train-of-four (TOF) stimulation, or the height of the single twitch (TH) was at least 20% of control before antagonism was attempted. Edrophonium has appeared less satisfactory when administered at lesser degrees of spontaneous recovery (Hughes, Astley and Payne, 1984; Engbaek et al., 1985; Lavery, Mirakhur and Gibson, 1985; Rupp et al., 1986).

In a recent study (Caldwell, Robertson and Baird, 1986) the reversal of profound unquantifiable neuromuscular blockade by neostigmine 0.07 mg kg^{-1} or edrophonium 0.8 mg kg^{-1} was investigated. The antagonists were administered 5 min after complete ablation of the evoked twitch response had been induced by vecuronium 0.1 mg kg^{-1} or atracurium 0.5 mg kg^{-1}. The study showed that, under those conditions, neostigmine was the more effective antagonist of both vecuronium- and atracurium-induced neuromuscular blockade. The present study is a logical extension of that described above in that, using a similar design, it compared the effect of neostigmine and edrophonium when administered at a quantifiable early point of spontaneous recovery (TH 5%).

PATIENTS AND METHODS

Thirty-nine patients gave informed consent to their inclusion in this ethically approved study. Premedication was with papaveretum 10–20 mg i.m. plus hyoscine 0.2–0.4 mg i.m. approximately 1 h before operation. Anaesthesia was induced using thiopentone 4–5 mg kg^{-1} i.v. and maintained with 67% nitrous oxide and 1% halothane (inspired) in oxygen. Supramaximal stimuli

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(0.1 Hz for 0.2 ms) were delivered via subcutaneous electrodes to the ulnar nerve at the wrist, and the resultant evoked response of the adductor pollicis muscle was transduced and recorded using the Myograph 2000 neuromuscular transmission monitor (Biometer, Denmark).

The first 20 patients received vecuronium 40–60 $\mu g\ kg^{-1}$ i.v. to achieve greater than 95% depression of TH. Tracheal intubation was performed once maximum depression of twitch height occurred, and IPPV instituted. When TH had recovered spontaneously to 5% of control, the patients were randomly selected to receive either neostigmine 0.07 $mg\ kg^{-1}$ plus atropine 1.2 mg i.v. or edrophonium 0.8 $mg\ kg^{-1}$ plus atropine 1.2 mg i.v. When TH exceeded 75% of control, the stimulation mode was changed to TOF and monitoring was continued until the TOF ratio reached 70%.

Measurements were made from the end of the injection of the antagonizing agent; T25 (time to TH of 25%); T75 (time to TH of 75%); recovery index (time from 25 to 75% TH) and Dur_{70} (time to a TOF ratio of 70%).

Using the same design, a further 19 patients were studied, neuromuscular blockade being induced by atracurium 150–200 $\mu g\ kg^{-1}$ i.v.

Statistical analysis of the results was by the Mann–Whitney *U* test. $P < 0.05$ was considered significant.

RESULTS

There were no differences in the physical characteristics of the patients studied (table I).

The initial antagonism of both vecuronium and atracurium, as measured by the T25, was more rapid following edrophonium than following neostigmine. In contrast, the recovery index, T75 and Dur_{70} were not different. The time interval from a TH of 75 to a TOF ratio of 70% ($T75–Dur_{70}$) was also analysed. This interval was significantly shorter in patients who received neostigmine compared with those who received edrophonium (tables II and III). The results are illustrated graphically in figure 1.

TABLE I. *Physical characteristics of patients*

		Neostigmine	Edrophonium
		Mean (SD)	Mean (SD)
Age (yr)	Vecuronium	41.0 (16.3) ($n = 10$)	35.1 (6.6) ($n = 10$)
	Atracurium	43.2 (14.7) ($n = 10$)	42.4 (15.4) ($n = 9$)
Weight (kg)	Vecuronium	65.5 (7.4) ($n = 10$)	63.8 (9.5) ($n = 10$)
	Atracurium	66.6 (12.7) ($n = 10$)	63.3 (5.1) ($n = 9$)

TABLE II. *Recovery times (mean ± SD (range)) (min) following the antagonism of vecuronium by neostigmine or edrophonium administered at twitch height 5% of control; measurements made from end of injection of reversal agent. T25 = Time to twitch height 25% of control; T75 = time to twitch height 75% of control;* Dur_{70} *= time to train-of-four ratio 70%;* $T75–Dur_{70}$ *= time from T75 to* Dur_{70}. **P < 0.01; *P < 0.05

	Neostigmine ($n = 10$)	Edrophonium ($n = 10$)
T25**	0.9 ± 0.2 (0.7–1.2)	0.6 ± 0.2 (0.3–0.8)
Recovery Index	2.2 ± 0.9 (1.0–3.3)	2.8 ± 2.5 (0.6–8.3)
T75	3.1 ± 1.0 (1.7–4.2)	3.4 ± 2.6 (1.0–9.0)
$T75–Dur_{70}$*	4.0 ± 3.1 (0.8–8.7)	11.6 ± 8.9 (2.8–28.3)
Dur_{70}	7.1 ± 3.3 (3.2–12.8)	15.0 ± 10.7 (3.2–34)

TABLE III. *Recovery times (mean ± SD (range)) (min) following the antagonism of atracurium by neostigmine or edrophonium. (Further explanation as table II)*

	Neostigmine ($n = 10$)	Edrophonium ($n = 9$)
T25**	1.5 ± 0.8 (1.0–2.2)	0.6 ± 0.2 (0.3–1.0)
Recovery Index	3.2 ± 0.8 (2.2–4.4)	4.5 ± 2.6 (0.4–8.8)
T75	4.7 ± 1.1 (3.2–6.3)	5.1 ± 1.0 (1.0–9.2)
$T75–Dur_{70}$*	4.3 ± 3.4 (0.2–11.2)	7.2 ± 2.3 (4.3–11.2)
Dur_{70}	8.9 ± 3.7 (4.2–16.0)	12.3 ± 3.8 (8.0–18.0)

DISCUSSION

The present study confirms that edrophonium had a more rapid onset of action (T25) than neostigmine. There was no difference in the recovery index. Subsequent recovery (from TH 75% to TOF 70%) was more rapid following neostigmine than following edrophonium. The

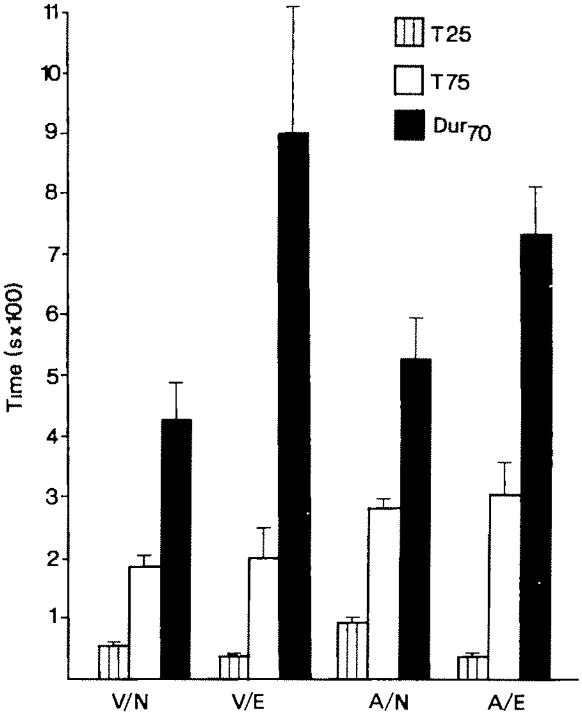

FIG. 1. Recovery times (mean ± SEM) for each combination of vecuronium (V), atracurium (A), neostigmine (N) and edrophonium (E) Times from end of injection of antagonizing agent (twitch height 5 %) to twitch height 25 % (T25) and 75 % (T75) and to a train-of-four ratio of 70 % (Dur_{70}).

total times from injection of reversal agent to satisfactory clinical recovery (TOF 70 %) were not statistically different. Edrophonium had a much more variable effect than neostigmine against vecuronium as suggested by the large standard deviations in Dur_{70} and T75–Dur_{70} in table II.

Engbaek and colleagues (1985) reported reversal of vecuronium at 10 % TH recovery and found that the time to achieve a TOF of 70 % was shorter following neostigmine 0.04 mg kg^{-1} than following edrophonium 0.75 mg kg^{-1}. This difference was abolished by using a larger dose of edrophonium (1.5 mg kg^{-1}). The dose ratio of edrophonium to neostigmine, 40:1, used by these authors, was greater than the previously reported equipotent ratio of between 12:1 and 16:1 (Baird, Bowman and Kerr, 1982; Cronnelly, Morris and Miller, 1982; Bevan et al., 1984). A further difference in technique between that study and the present one is that Engbaek and his colleagues (1985) used a continuous i.v. infusion of neuromuscular blocking agent.

Many authors have studied the antagonism of neuromuscular blockade by edrophonium, and neostigmine. However, the results are difficult to compare because of the different anaesthetic, stimulating and recording techniques used. In addition, the level of TH recovery when the antagonist is injected and the selected end-point of satisfactory recovery, vary considerably from one study to the next. For example, although Rupp and co-workers (1986) also showed that, when antagonizing vecuronium-induced neuromuscular blockade at less than 10 % TH recovery, increasing the dose of edrophonium from 0.5 mg kg^{-1} to 1 mg kg^{-1} abolished the delayed recovery of neuromuscular transmission when compared with neostigmine 0.04 mg kg^{-1}, their study only looked at recovery to a TH of 90 %. The present study showed no difference in the total recovery times following edrophonium 0.8 mg kg^{-1} or neostigmine 0.07 mg kg^{-1}, but when the constituent phases of recovery were examined in more detail (tables II and III), differences began to emerge which may be of importance in clinical practice.

A TH of 5 % is close to the first clinically detectable recovery of neuromuscular transmission using TH or TOF stimulation modes. A TOF ratio of 70 % is widely accepted as the desired end-point of clinical recovery. These are the starting and end-points in the present study. It has been demonstrated that patients with protected airways are usually able to ventilate adequately before TH has recovered to 75 % of control (Hackett, Hughes and Payne, 1986). The present study shows that the times from a TH recovery of 75 % to a TOF ratio of 70 % are longer (up to 28 min) following edrophonium than following neostigmine (up to 8 min). If patients are discharged from theatre merely when spontaneous ventilation appears adequate, they may be "at risk" during this T75–Dur_{70} period.

If the selected recovery end-point falls within the initial rapid effect of edrophonium, then edrophonium will appear more effective than neostigmine. The more consistent and sustained effect of neostigmine against both vecuronium and atracurium has been previously demonstrated (Caldwell, Robertson and Baird, 1986). These results, along with those of the present study, suggest that neostigmine is the preferred antagonist.

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CANNULATION OF THE RADIAL AND DORSALIS PEDIS ARTERIES

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SUMMARY

The complications inherent in cannulation of the radial (group I) and dorsalis pedis (group II) arteries were studied in 46 patients. All the local and systemic variables which might be considered to contribute to damage of the artery were studied, from which it appeared that only the duration of cannulation, prothrombin time and partial thromboplastin time were significant in determining post-cannulation blood flow. A 20-gauge Teflon cannula was used in all patients and velocity of flow measured with a Doppler velocimeter probe. A majority of arteries showed a reduction of flow velocity for 24–72 h after the removal of the cannula, with evidence of improvement at 120 h. In six arteries—three in each group—flow ceased altogether after 24–72 h. No disability of either hand or foot resulted.

Percutaneous arterial cannulation is now the definitive method of monitoring arterial pressure during critical procedures such as deliberate hypotension, extracorporeal circulation, and neurosurgical operations in the sitting position. Attention focused initially on the radial artery, rather than the brachial, as Allen's test could be used to establish the adequacy of the collateral blood supply to the hand. The dorsalis pedis artery proved a useful and often more convenient alternative (Youngberg and Miller, 1976). Although there is a substantial literature on the technique and morbidity of radial artery catheterization (Bedford and Wollman, 1973; Bedford, 1977; Davis, 1978; Davis and Anzult, 1979; Davis and Stewart, 1980), comparatively little is available on the dorsalis pedis approach (Johnstone and Greenhow, 1973; Youngberg and Miller, 1976). Further, the published studies were concerned primarily with the size of the cannula and the duration of cannulation in relation to thrombosis and infection; little attention has been paid to other factors which might be expected to result in complications, such as the patient's coagulation profile, and serum cholesterol and triglyceride concentrations.

The present study compared the effect of cannulating the radial and dorsalis pedis arteries and explored the possible correlation of impaired flow after removing the cannula with the variables mentioned.

PATIENTS AND METHODS

Forty-six adult patients undergoing elective surgery were studied. Patients with a history of diabetes mellitus, hypertension and peripheral vascular disease, and those receiving vasopressor or anticoagulant therapy were excluded from the study. Estimation of fibrinogen concentration, prothrombin time (PT), partial thromboplastin time (PTT), and serum cholesterol and triglyceride concentrations was carried out in all patients before surgery.

Patients were randomly allocated to two groups, and had either their radial (group I) or their dorsalis pedis (group II) artery cannulated. The adequacy of the collateral blood supply to the hand was evaluated (group I) before operation using the

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modified Allen's test (Allen, 1929; Oh and Davis, 1975). The result was graded as: grade 1 = normal, 0–7 s "flush time"; grade 2 = equivocal, 8–14 s; grade 3 = poor or abnormal, longer than 15 s.

Velocity of blood flow was determined before cannulation in all patients with a bi-directional (forward and reverse flow) Doppler velocimeter probe with recorder and memoryscope ("Vasoflo 2" non-invasive vascular laboratory, Sonicoid). Peak systolic velocity (forward flow) and maximum diastolic velocity (reverse flow) were measured from the calibrated chart record in cm s^{-1}.

All cannulations were performed by one investigator in the operating room after careful scrubbing, but without gloves. The skin of the patient was prepared thoroughly with alcohol swabs. A 20-gauge non-tapered Teflon cannula (Angiocath) was inserted directly percutaneously as for an i.v. cannulation. This was taped, but not sutured, in place and no topical antibiotic was applied.

During the period of cannulation all cannulae were flushed continuously at 3 ml h^{-1} with saline containing heparin 2 u. ml^{-1}. Details of arterial cannulation were recorded, including the site, the number of times the artery was punctured and whether or not a haematoma was present.

After the catheter was removed, pressure was applied for 5 min. The distal and proximal catheter segments were clipped under sterile conditions and dropped separately into two sterile containers. Proximal and distal ends of the catheter were cultured separately on cooked meat media or thioglycollate broth incubated at 32 °C and examined for growth after 24 and 48 h. If no growth was found, a subculture was made on blood agar plates incubated both aerobically in 5% carbon dioxide and anaerobically at 35 °C for 24 h. Any growth was identified and tested for antibiotic sensitivity.

All patients were examined immediately after decannulation by one investigator and the velocity of the flow was recorded by the ultrasonic probe just distal to the site of cannulation. The direction of flow (forward or reverse) was determined from the paper trace and the peak velocity was measured for both flows. These flow studies were repeated after 24, 72 and 120 h. At the time of removal, the patency of the cannula was noted and the site inspected for evidence of infection, haematoma or discolouration of the surrounding skin.

Statistics

Results are expressed as mean (±SD). Unpaired Student's t test was used to test the differences between two sample means, and Chi-square or Fisher's exact test for homogeneity where appropriate. Values of $P < 0.05$ were considered to be statistically significant.

In an attempt to predict which variables appeared to be important in contributing to any reduction in the velocity of flow, multiple linear regression techniques were used. The independent variables were age, Allen's test (in radial artery group), number of attempts at arterial puncture, duration of cannulation, fibrinogen concentration, prothrombin time (PT), partial thromboplastin time (PTT), and serum cholesterol and triglyceride concentrations. These independent variables were regressed on the difference between velocity of the flow before cannulation and that immediately after removal as well as at 24, 72 and 120 h after removal. Several approaches were used to select the best regression model for each variable (step-wise, forward selection, backward selection). The data were loaded on a mainframe 4361 IBM Computer Model 5 and the statistical analysis (SAS) package used.

RESULTS

Patients in both groups were comparable with respect to age and sex distribution (table I).

Fibrinogen concentrations were slightly but significantly higher in group I ($P < 0.05$), but the results of the rest of the laboratory investigations were within their normal ranges (table II).

Table III shows that 17 patients (68%) in group I had good collateral flow before cannulation (Allen's test grade 1) and eight patients (32%) had diminished flow (Allen's test grade 2).

The numbers of arterial punctures were 1.8±0.9 and 1.6±0.7 (mean±SD) in groups I and II, respectively. The duration of cannulation

TABLE I. *Demographic data*

	Group I: radial artery (n = 25)	Group II: dorsalis pedis artery (n = 21)
Age (yr)	38.6±14.7	37.7±13.7
Sex (M/F)	18/7	15/6

TABLE II. *Fibrinogen, cholesterol and triglyceride concentrations, and PT and PTT values before operation. * Fibrinogen concentration was significantly greater in group I than in group II; there was no significant difference in the other variables. † Normal limits*

	Group I: radial artery	Group II. dorsalis pedis artery
Fibrinogen (200–400 mg dl^{-1})†	411.4±170*	337.1± 116
Cholesterol (120–280 mg dl^{-1})†	134.6±37	174.6±55
Triglyceride (30–180 mg dl^{-1})†	102±50	84.6±40
PT (s)	13.1±1.9	12.4±1.1
PTT (s)	26.4±5.6	24.1±5

TABLE III. *Allen's test before cannulation of radial artery*

	Grade 1	Grade 2	Grade 3
No. patients (%)	17 (68%)	8 (32%)	0
Flush time (s)	5.2±1.2	9.7±1.5	—

in the dorsalis pedis group was longer, but not significantly so (tables IV and V).

Three patients in each group developed complete occlusion of their vessels. In group I, radial artery occlusion occurred 72 h after decannulation in all three. In group II, dorsalis pedis thrombosis

TABLE IV. *Changes in the peak systolic (forward) velocity values (cm s^{-1}) in group I. The reductions in the forward flows were significant 24 h (P < 0.01) and 72 h (P < 0.025) after decannulation compared with the precannulation values*

		Forward flow				
Patient No.	Duration of cannulation (h)	Before cannulation	Immediately after decannulation	24 h after decannulation	72 h after decannulation	120 h after decannulation
1	50	25	21	20	20	23
2	90	18	17	15	0	0
3	33	21	10	12	15	20
4	40	6	6	6	0	0
5	26	20	18	15	16	19
6	27	23	10	12	14	20
7	26	20	20	18	20	20
8	26	20	20	16	17	17
9	60	12	12	10	12	15
10	47	20	20	18	18	20
11	1.5	20	20	10	10	15
12	4	20	20	20	20	20
13	1.5	20	20	20	20	18
14	4.5	21	18	14	21	21
15	2	23	23	23	23	24
16	1	15	15	15	15	15
17	19	21	21	15	10	22
18	22	15	14	14	10	0
19	3	30	30	28	28	25
20	22	18	18	18	17	18
21	1	15	15	7	7	14
22	6	20	18	12	18	20
23	7.5	23	23	23	23	23
24	20	20	20	20	18	18
25	6	20	20	20	20	20
Mean±SD	21.8±22	19.4±4.5	17.9±4.9	16±5	15.6±6.7	17±7.0

TABLE V. *Changes in the peak systolic (forward) velocity values* ($cm\ s^{-1}$) *in group II. There were significant reductions in the forward flow 24 h* ($P < 0.01$) *and 72 h* ($P < 0.05$) *after decannulation compared with the precannulation values*

		Forward flow				
Patient No.	Duration of cannulation (h)	Before cannulation	Immediately after decannulation	24 h after decannulation	72 h after decannulation	120 h after decannulation
1	27	18	17	14	16	18
2	26	32	32	30	32	32
3	28	17	17	0	0	0
4	140	25	15	15	20	24
5	50	30	30	30	30	30
6	80	20	16	12	20	20
7	25	20	9	0	0	0
8	115	33	23	23	30	33
9	34	30	15	10	0	10
10	30	8	8	8	7	8
11	96	13	12	9	13	13
12	2.5	21	18	13	10	5
13	20	18	18	18	18	18
14	5	15	15	15	15	15
15	22	11	6	4	0	0
16	2	19	19	15	20	20
17	20	16	15	13	14	16
18	3	13	10	8	13	13
19	6	18	18	17	18	18
20	4.5	16	15	14	14	15
21	14	15	15	15	14	15
Mean ± SD	35.7±39	19.4±6.9	16.3±6.2	13.4±7.8	14.4±9.5	15.3±9.6

occurred 24 h after decannulation in two patients and 72 h after decannulation in the third patient. The incidence of decreases in forward flow (peak systolic velocity) after 24 h was significantly higher ($P < 0.05$) in the dorsalis pedis group. Fifteen patients (71%) in the latter group had variable degrees of reduction in forward flow and it was significant 24 h ($P < 0.01$) and 72 h ($P < 0.05$) after decannulation compared with the pre-cannulation values. In the radial artery group, 16 patients (64%) also showed variable degrees of reduction in forward flow which were significant at 24 h ($P < 0.01$) and 72 h ($P < 0.025$) after decannulation when compared with pre-cannulation values (tables IV and V).

There was no correlation between the abnormality of Allen's test and the decrease in the flow after decannulation. Reduction in the flow in both groups was not related to sex difference.

Multiple regression analysis showed that the decrease in forward flow velocity was significantly related to the duration of cannulation in both groups. Furthermore, the contributions of PT and PTT were significant. Two-sample regression equations will be discussed later.

There were no significant changes in the reverse flows (maximum diastolic velocities) in either group when compared with the pre-cannulation values (table VI).

No patient developed bruising or signs of impaired perfusion of the hand or foot during or following cannulation and all cannulae were patent at the time of removal.

Staphylococcus epidermidis was isolated from the catheter tip in four instances in each group. The durations of cannulation in these patients were 25.1±21.4 h (radial artery) and 54.7±21.4 h (dorsalis pedis artery). The incidence of positive culture from the hub was greater and *S. epidermidis* was isolated in 14 patients (56%) and 10 patients (47.6%) in the radial artery and dorsalis pedis group, respectively. In addition, *Streptococcus faecalis* and *Proteus* species were isolated from two catheter hubs in the radial artery group. No patient developed bacteraemia or septicaemia. There was no correlation between the incidence of occlusion or flow impairment and the occurrence of infection in either group.

TABLE VI. *Changes in the maximum diastolic velocity (reverse flow) values (cm s^{-1}) in groups I and II. There were no significant changes in the reverse flow compared with the precannulation values*

	Reverse flow				
	Before cannulation	Immediately after decannulation	24 h after decannulation	72 h after decannulation	120 h after decannulation
Group I	4.2±2.7	3.4±2.5	3.3±2.9	4.4±3.0	4.3±2.7
Group II	7.6±2.6	6.6±3.9	5.9±4.6	6.0±4.3	3.9±4.3

DISCUSSION

Studies on percutaneous radial artery cannulation vary widely in the reported incidence of complications. Current evidence indicates that both the type and size of cannula used, and the duration of cannulation are important factors in determining the incidence of post-cannulation thrombosis. Using 15-gauge Teflon cannulae, Little, Clarke and Shanks (1975) reported complete occlusion of the radial artery in 22 out of 41 cannulations (54%) and, of these, 13 developed features of mild ischaemia. The reported incidence of radial artery occlusion following cannulation with 20-gauge Teflon cannulae varied from 0% to 21% (Davis, 1978; Kim, Arakawa and Bliss, 1975). Bedford and Wollman (1973) noted a definite relationship between the duration of cannulation and arterial occlusion. Youngberg and Miller (1976), using 20-gauge Teflon cannulae, reported a 6.7% incidence of thrombosis following dorsalis pedis artery cannulation for less than 24 h; one of the patients, however, had evidence of ischaemia in his foot.

In the present study, using 20-gauge Teflon cannulae, three patients (12%) in the radial artery group and three (14%) in the dorsalis pedis group had complete occlusion of their vessels. This occurred 72 h after decannulation in the radial artery group and 24 h after decannulation in two patients in the dorsalis pedis group.

A progressive reduction in forward flow was observed in both arteries after decannulation, and this appeared to show some recovery after 72–120 h, although the differences (tables IV and V) were not significant. The reduction in forward flow in the dorsalis pedis artery was significantly greater than that in the radial artery at 24 h only ($P < 0.05$). However, it is important to note that the transcutaneous continuous-wave Doppler instruments measure velocity of flow rather than volume of flow.

We found no correlation between the abnormality of the Allen's test and the reduction of flow after decannulation. Slogoff, Keats and Arlund (1983) reported that cannulation of the radial artery in patients with abnormal Allen's tests did not result in abnormal flow or ischaemia. Therefore, the value of Allen's test as a predictor of ischaemia should be questioned.

Our findings showed no correlation between sex and the incidence of occlusion. This agrees with Davis and Stewart (1980), although Kim, Arakawa and Bliss (1975) and Slogoff, Keats and Arlund (1983) found a correlation between female sex and the incidence of arterial occlusion.

All approaches of the multiple regression analysis were consistent and yielded the same set of models for each of the dependent variables. In the radial artery group, the best five model variables found for the changes in the forward flow after 72 h were selected on the basis of inclusion of many independent variables and on the significant improvements of the r^2 value over the best four model variables. The sample regression equation for the difference in the forward flow velocity (cm s^{-1}) before cannulation and 72 h after decannulation was:

$$\begin{aligned}&5.142+0.336\times\text{duration of Allen's test (s)}\\&+0.866\times\text{number of attempts at arterial puncture}\\&+0.115\times\text{duration of cannulation (h)}\\&-0.9\times\text{PT (s)}\\&+0.173\times\text{PTT (s)}\end{aligned}\qquad(1)$$

where the partial regression coefficient of the duration of cannulation was significantly greater than zero ($P = 0.0065$) and that for PT was significantly smaller than zero ($P = 0.05$). The other independent variables in equation (1) were not significantly different from zero. In this model, age, fibrinogen concentration, cholesterol concentration and triglyceride concentration were not included.

In the dorsalis pedis group, the change in forward flow immediately after decannulation was the only valid statistical and clinical model and the best six model variables were selected. The sample regression equation for the changes in the forward flow velocity (cm s^{-1}) at that time was:

$$\begin{aligned}&20.872+0.09\times\text{age (yr)}\\&-2.112\times\text{number of attempts at dorsalis pedis puncture}\\&+0.062\times\text{duration of cannulation (h)}\\&-0.0251\times\text{cholesterol concentration (mg dl}^{-1})\\&-0.044\times\text{triglyceride concentration (mg dl}^{-1})\\&-0.492\times\text{PTT (s)}\qquad(2)\end{aligned}$$

where the partial regression coefficient of "duration of cannulation" was significantly greater than zero ($P = 0.02$) and that for "PTT" was significantly smaller than zero ($P = 0.01$). The multiple regression techniques used in this study substantiate that the cholesterol, triglycerides and fibrinogen concentrations, age, duration of Allen's test and the number of attempts at arterial cannulation were not of any predictive value in the occurrence of flow abnormalities.

The two equations presented are the result of both statistical and non-statistical considerations (Daniel, 1983) and can be utilized to predict the likelihood of changes in the velocity of the flow after decannulation. Further studies are needed to estimate the accuracy of these equations. The reduction of forward flow velocity was significantly related to the duration of arterial cannulation in the radial artery group ($P = 0.0065$, equation (1)) and the dorsalis pedis group ($P = 0.02$, equation (2)). This finding agrees with other reports by Bedford and Wollman (1973) and Evans and Kerr (1974). This can also explain the higher incidence of decreased velocity of the flow in the dorsalis pedis group in this study. This group had the artery cannulated for a mean period of 35.7 h compared with 21.8 h in the radial artery group—although this difference was not significant. Increased PT and PTT decreases the likelihood of forward flow reduction.

Davis and Anzult (1979) reported a 39% incidence of contamination of radial artery catheters, and Band and Maki (1979) demonstrated an 18% colonization rate of arterial catheters and a 4% incidence of bacteraemia. Adams, Speer and Rudolph (1980) reported a 25% colonization rate of arterial catheters with only a 0.6% rate of bacteraemia. He found no correlation between incidence of infection and duration of cannulation. In this study, we cultured both the distal end, which is linked to colonization within the blood, and the proximal catheter, which is linked to skin colonization. Maki, Weise and Sarafin (1977) suggested that most blood stream infections occur from skin colonization. In our study, the catheter contamination rates were 16% and 19% in groups I and II, respectively—values lower than those reported previously after arterial or venous catheterization (Fuchs, 1971; Band and Maki, 1979; Davis and Anzult, 1979). No patient developed bacteraemia and no correlation was found between the incidence of infection and the impairment of flow. The incidence of hub colonization was greater in the radial artery group (56%) than in the dorsalis pedis group (48%). Hoyt (1984) in a review of factors contributory to infection suggested that no arterial catheter should be left in place for longer than 4 days because of the strong correlation between duration of cannulation and colonization and bacteraemia.

In conclusion, this study demonstrated that percutaneous dorsalis pedis arterial cannulation provided a suitable alternative to the radial artery. Using 20-gauge Teflon cannulae, we found no major complication associated with the cannulation of either artery. Our findings suggest that cholesterol, triglyceride and fibrinogen concentrations, age of the patient, an abnormal Allen's test and the number of arterial punctures are not of significant value in predicting the occurrence of abnormalities of flow following the removal of the cannula. We found that the incidence of impaired flow after decannulation was directly related to the duration of cannulation and inversely related to plasma PT and PTT values.

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BLOCKADE OF CONTRALATERAL CAROTID SINUS NERVE ENHANCES IPSILATERAL NERVE ACTION POTENTIALS UNDER HALOTHANE ANAESTHESIA

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SUMMARY

In 10 dogs, one carotid sinus was isolated from the systemic circulation without disturbing its sympathetic innervation. The isolated sinus was connected to a servo-controlled pressure generator which kept mean intrasinus pressure, pulse pressure, and frequency of pulsation constant. The carotid sinus baroreceptor nerve action potentials (NAP) were measured, together with the intransinus and systemic pressures. Following control measurements, the end-tidal concentrations of halothane in oxygen were varied between 0.0 and 2%, in random increments of 0.5%, each with 30 min of stabilization. The carotid sinus NAP response to halothane was biphasic in a dose-dependent manner. The series was repeated after neural blockade of the contralateral sinus with 1% lignocaine 2–3 ml. This blockade enhanced all NAP responses (P < 0.001), suggesting that a central inhibitory effect, initiated by the contralateral sinus, had been removed.

Halothane is often used in the anaesthetic management of patients undergoing major cardiovascular procedures such as carotid endarterectomy. Patients with carotid artery disease may show poor adaptive responses to sudden haemodynamic changes, both under halothane anaesthesia and in the recovery room (Angell-James and Lumley, 1974). Therefore, the regulation of arterial pressure under halothane anaesthesia, and its effect on baroreceptor function, are of considerable clinical interest and have been studied extensively.

The regulation of arterial pressure by the baroreceptor reflex involves an integrated, negative-feedback mechanism which operates as a servo-control system. This feature makes it possible for the regulating mechanism to compensate rapidly for the sudden changes in normal arterial pressure (Korner, 1971; Kirchheim, 1976).

Several investigators have attempted to delineate the mechanism of the central integration of baroreceptor afferents and their relative contribution to the overall regulation of arterial pressure. Using closed- or open-loop techniques, with or without nerve recording, these studies have shown that the combined effect of pressoregulatory signals from the carotid sinus and aortic arch baroreceptors may exhibit facilitatory (synergistic), inhibitory (occlusive), or additive (no relation) summation (Angell-James and Daly, 1970; Donald and Edis, 1971; Ishikawa and Sagawa, 1983). The type of central summation seen depends, in part, on the initial input intensity of the receptors (Ishikawa and Sagawa, 1983).

Previous studies of the effect of halothane anaesthesia on the reflex modulation of baroreceptor function have produced divergent results. Some investigators have reported that halothane-induced modification of baroreceptor function in the dog is mediated via its effect on the central nervous system (Price, Linde and Morse, 1963; Price, Price and Morse, 1965; Behnia and Koushanpour, 1984). Others, also using the dog,

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have emphasized that this effect is peripheral, and is mediated by local sensitization of the peripheral baroreceptors (Epstein, Wang and Bartelstone, 1968; Seagard et al., 1983). Although other studies in cats, rabbits, and dogs have shown that the inhalation of 1–3% halothane produced increases in the number of action potentials in the carotid sinus nerve over a wide range of applied pressure (Biscoe and Millar, 1964), the same dose of halothane had no detectable effect on the discharge rate of the aortic baroreceptors (Aars and Hauge, 1972).

These discrepancies may be attributable either to species differences, or to differing experimental techniques; for example, in those studies in which a peripheral effect was seen (Seagard et al., 1983), the carotid sinus nerve had been cut, thereby removing its connection with the ponto-medullary centre.

An important and related question is the nature of the interactive effect of the function of the contralateral baroreceptor on function in the ipsilateral baroreceptor. Surgical and experimental elimination, or stimulation, of the individual carotid or aortic baroreceptors may lead to an increase, or decrease, in the activity of the remaining baroreceptors (Koch, 1931; Angell-James and Lumley, 1974; Ishikawa and Sagawa, 1983). A recent study (Felder, Heesch and Thames, 1983), in dogs anaesthetized with thiopentone and alpha-chloralose, has demonstrated that occlusion of the contralateral common carotid artery caused a significant increase in activity in the ipsilateral carotid sinus nerve. However, the process of central summation of bilateral carotid sinus nerve activity under halothane anaesthesia has not been investigated.

The present study was designed to determine whether blockade of the contralateral carotid sinus nerve (with 1% lignocaine) would alter the responses of the ipsilateral sinus nerve action potentials (NAP) during halothane anaesthesia. The NAP were recorded from a whole nerve with intact connection to the ponto-medullary centre, and when the intrasinus pressure, pulse pressure, and frequency of pulsation were kept constant and close to normal values by a servo-controlled pressure generator. This pulsatile system was chosen as it activates a population of fibres that fires in a pulse phasic pattern characteristic of arterial baroreceptors and minimizes chemoreceptor activities.

MATERIALS AND METHODS

Anaesthesia and monitoring

Ten conditioned mongrel dogs of either sex, weighing between 20 and 25 kg, were used in this study. The criteria for selection were normal arterial pressure, blood cell count, and urine analysis, and the absence of microfilaria. Anaesthesia was induced with sodium pentobarbitone 30 mg kg^{-1} i.v. During the period the dogs were not receiving halothane, surgical anaesthesia was maintained by an i.v. infusion of pentobarbitone at a rate of 2 mg kg^{-1} h^{-1} from a model 341A syringe pump (Orion Research, Inc., Cambridge, MA). The cumulative total dose of pentobarbitone used in each dog ranged from 650 to 700 mg. Although the basal level of pentobarbitone anaesthesia used in this study may have had a CNS effect, this would affect responses from both the intact and blocked contralateral carotid sinuses and, hence, was neglected insofar as carotid sinus function was concerned. The animals were ventilated through a tracheal tube with 100% oxygen to minimize chemoreceptor stimulation and contamination of the recorded baroreceptor action potentials. Ventilation via a semi-closed circle system with carbon dioxide absorption was adjusted by varying the tidal volume from approximately 275 to 350 ml and the frequency from 12 to 16 b.p.m. to maintain end-tidal carbon dioxide at 5% (Datex capnograph, model CD-100: Instrumentarium Oy Espoo, Finland). The oesophageal temperature was kept at 36 ± 1 °C with the aid of a warming blanket and heating lamp.

A polyethylene catheter was inserted with its tip near the carina, for determination of the end-tidal carbon dioxide and halothane concentrations. The left femoral vein was cannulated to permit the infusion of drugs and the replacement of fluid. The right femoral artery was cannulated to permit measurement of systemic arterial pressure (SAP) (calibrated Statham P50 miniature pressure transducer coupled with a Statham model SP 1400 pressure monitoring system (Statham Instruments Divisions, Gould, Inc., Oxnard, CA)), and the withdrawal of blood for blood-gas analyses.

Surgical preparation

Following bilateral neck dissection, the right or left carotid sinus area of each dog was selected randomly and exposed under a Zeiss operating microscope. The baroreceptor branch of the

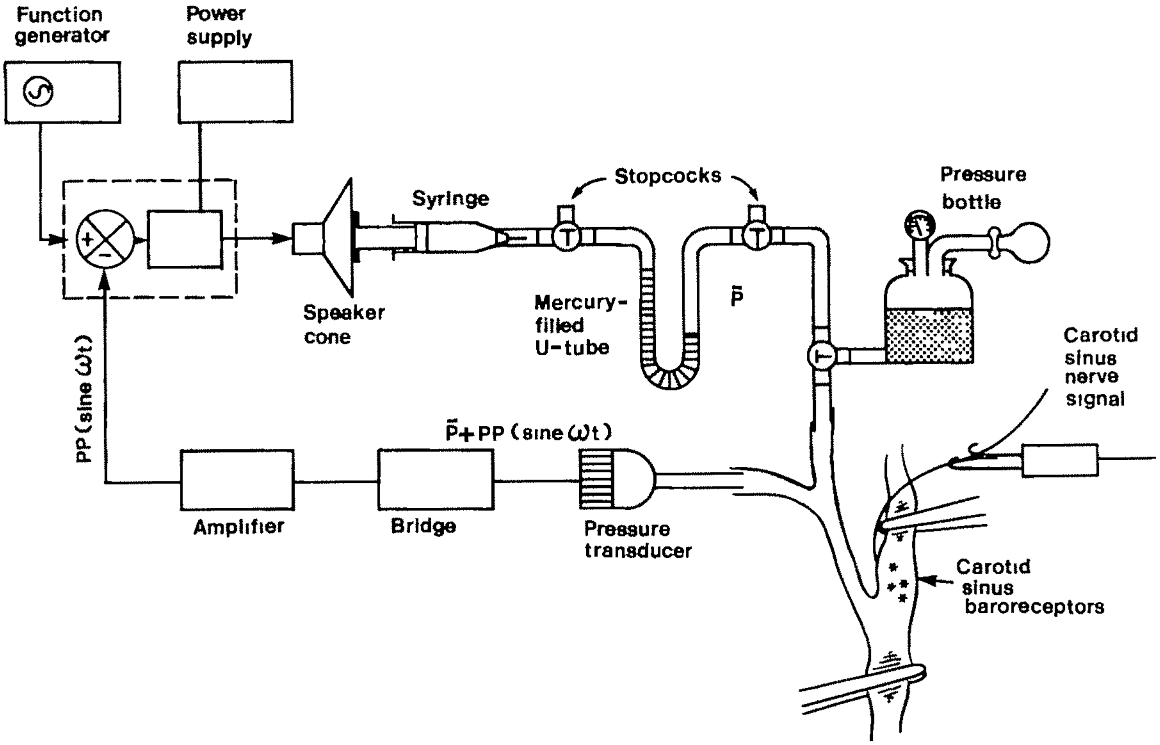

FIG. 1. Schematic diagram depicting the servo-controlled pressure generator, and the layout of the study of the effect of halothane on carotid sinus nerve action potential with the contralateral sinus intact or blocked with 1% lignocaine 2–3 ml.

carotid sinus nerve was located and identified by audibly monitoring the phasic relation of the spike frequency to the pulse pressure. Except for being placed on the electrode, the nerve was not subjected to any additional handling and the nerve sheath was left intact. Insofar as was possible, the physiological integrity of the whole baroreceptor nerve was preserved. Care was taken not to disturb the sympathetic innervation to the carotid sinus (Koushanpour and Kelso, 1972). On the contralateral side, a catheter was positioned visually in the neck with its tip in the proximity of the carotid sinus nerve, for later administration of 1% lignocaine 2–3 ml. The carotid sinus nerve, as described above, was left undisturbed.

The occipital, the ascending pharyngeal, and all collateral arteries of the carotid sinus were ligated. The lingual artery was cannulated with a 20-gauge catheter to obtain baseline determinations of carotid sinus mean pressure, sinus pressure wave form, pulse amplitude, and pulse frequency. Control values for arterial pressure and heart rate were determined during a 15-min period after a sufficient period of haemodynamic stability. These values were then used to adjust the function of the servo-controlled pressure generator which perfused the haemodynamically isolated carotid sinus. This perfusion system simulated the optimum physiological haemodynamic variables necessary for modulation of carotid sinus nerve action potentials.

As depicted schematically in figure 1, the carotid sinus was functionally isolated from the dog's circulatory system and was connected to a servo-controlled pressure generator designed by Spickler and Koushanpour (1968). This system consisted of a 20.3-cm, 20-W loudspeaker with a 19-mm excursion. The movement of the speaker diaphragm drove a 10-ml glass syringe which served as a perfusion pump. The glass syringe was connected through a three-way stopcock to a glass U-tube (2 mm i.d.) half-filled with mercury. The other end of the U-tube was connected through a second stopcock to the external carotid artery with a polyethylene catheter through which the carotid sinus was perfused. A pressure bottle containing oxygenated lactated Ringer's solution warmed to 37 °C was used to introduce steady pressures to the system at the second stopcock, independent of the excursion of the syringe pump. During isolation and perfusion of the carotid sinus, care was taken to maintain the *in situ* length of the carotid sinus segment, thereby preserving its physiological functional distensibility.

Carotid sinus pressure was measured by a calibrated P50 Statham miniature pressure transducer and amplified by a Dymec D-C amplifier, model 2460A. A second Statham transducer connected to this system produced a feedback signal for controlling the syringe pump. Using a function generator, sinusoidal wave forms with a frequency of 2.5–3 Hz, and an amplitude of 45–50 mm Hg were superimposed on a steady intrasinus pressure throughout each investigation. Therefore, the excursion of the loudspeaker was controlled by a feed-back loop from the pulsatile pressure developed within the carotid sinus to produce intrasinus pressure, pulse pressure, and frequency of pulsation, which simulated the baseline values of the intact non-isolated carotid sinus. The haemodynamic stability of the preparation was continuously assessed by monitoring systolic arterial pressure. On average, the entire investigation on each animal lasted between 7 and 8 h.

Data acquisition

The design of the study consisted of simultaneous recordings of the systemic arterial pressure, carotid sinus pressure (CSP), and baroreceptor nerve action potentials (NAP) from a whole intact nerve before and after blockade of the contralateral carotid sinus with 1% lignocaine 2–3 ml, and at different end-tidal halothane concentrations. The whole baroreceptor NAP was recorded by placing the intact carotid sinus nerve across a bipolar platinum hook electrode with its poles spaced 2 mm apart. The nerve preparation was covered with mineral oil previously warmed to 37 °C. The nerve signal was amplified successively by a Grass Model P15 differential AC microelectrode preamplifier (Grass Instruments, Quincy, MA) with a passband of 100–3000 Hz, and a Tektronix FM 122 differential amplifier (Tektronix, Inc., Beaverton, OR) with a passband of 80–10000 Hz. The amplified signal provided a suitable input voltage for recording the NAP along with the SAP and the CSP on a Sanborn Model 3907A FM analogue tape recorder (Hewlett–Packard, Palo Alto, CA). Data were recorded at a speed of 38 cm s^{-1} for subsequent computer analysis.

After control measurements, halothane was given to each dog with the contralateral carotid sinus intact. End-tidal concentrations of halothane were established at random in steps of 0.0, 0.5, 1.0, 1.5, and 2.0% in oxygen and maintained for 30 min before making measurements. Halothane concentration was measured continuously by an Engstrom Emma model C22.2 NO.125 anaesthetic analyser (Engstrom Medical AB, Sweden). End-tidal concentrations of halothane were also determined periodically with a model 8000 gas chromatograph (Basic Gas Chromatograph, Carle Instruments, Inc., Anaheim, CA). Carotid sinus NAP, CSP and SAP were recorded on magnetic tape for 2 min at the end of each exposure to the different halothane concentrations. A second 2 min of data recording was made 10 min later. Since the frequency of pulsation of the intrasinus pressure generated by the servo-controlled pressure pump was set at about 3 Hz, and we recorded 2 min of data at each halothane concentration, this yielded a total of 360 cycles of pressure and nerve over which calculations were made. These records were used for subsequent analyses.

At the end of a given series with the contralateral sinus nerve intact, the halothane was discontinued and 30–40 min allowed for recovery from halothane. When the halothane concentration was near zero (less than 0.01%), another carotid sinus NAP was recorded to determine whether the NAP had returned to its baseline value. At this time the contralateral carotid sinus was blocked with 1% lignocaine 2–3 ml and halothane was given at random to establish the previously described end-tidal concentrations. Carotid sinus NAP, CSP, and SAP were recorded for 2 min at the end of each exposure to the different halothane concentrations. A second 2-min recording was made 10 min later. The nerve and pressure data thus obtained were analysed as described below.

Data analysis

Quantitation of whole baroreceptor nerve signal. The action potentials recorded from the carotid sinus nerve in this study represent activity in the whole intact baroreceptor nerve. They exhibit a distinct modulation of both frequency and amplitude of spikes during the application of the pulsatile pressure generated by the servo-controlled pressure generator. Spike amplitude modulation may be considered as a measure of temporal summation (recruitment) for those units firing in phase and at the same frequency. Since the frequency of spikes in a single baroreceptor nerve fibre is considered the most significant measure of nerve activity, and since nerve action potentials in our study were recorded from a multifibre preparation, we calculated the integrated electrical activity of the whole baroreceptor nerve action potentials as a measure of the baroreceptor nerve output using the technique developed by Koushanpour and McGee (1968). Briefly, this technique which is called "demodulation", involved rectifying the recorded action potentials and electrically integrating the resulting signal. This demodulation procedure represented the sum of activity of all those units which were firing both in phase and out of phase. The nerve and pressure signals were digitized from the analogue data stored on magnetic tape by a PDP-12A analogue-to-digital converter at 300 samples s^{-1} for subsequent statistical analysis of the data.

Data reduction

To eliminate within- and between-dog variations, the pressure and nerve data were treated as follows. For each dog, the computed nerve activities and pressure values were plotted as a function of different end-tidal halothane concentrations. Since these plots yielded a similar pattern of relationships for all investigations, indicating that the dogs all belong to the same population, the data for each dog were first normalized and then combined with similar data from other dogs to obtain a pooled relationship.

Normalization procedures were performed for each dog, with the digitized nerve data for a given end-tidal halothane concentration expressed as a fraction (ratio) of the mean of the control values. To calculate this ratio, the values of the nerve action potentials corresponding to a given halothane concentration were divided by the mean nerve action potentials recorded with zero end-tidal halothane concentration. These values were then averaged for each halothane group for all experiments to obtain the mean (±SD) for the nerve response to a given end-tidal halothane concentration at the constant CSP produced by the servo-controlled pressure generator in each investigation. The plotted data thus obtained were used to construct the relationship between the carotid sinus NAP and halothane concentrations, while the contralateral carotid sinus was either intact, or blocked with 1% lignocaine 2–3 ml. These data were used to determine the relative contribution of the contralateral carotid sinus to the function of the ipsilateral carotid sinus with and without halothane anaesthesia. Two-way analysis of variance was performed for statistical analysis of the data.

RESULTS

Effect of halothane on haemodynamic indices

After blockade of the contralateral sinus nerve the SAP increased from 115±18 mm Hg to 130±15 mm Hg and within 2–3 min it stabilized at 122±20 mm Hg. Table I shows the changes in arterial pressure associated with the different concentrations of halothane—before and after the blockade of the contralateral carotid sinus nerve. There was an insignificant increase in systemic arterial pressure following blockade of contralateral sinus nerve at 0.0, 0.5, and 1% halothane concentrations.

The servo-controlled pressure generator was adjusted to keep, for all experiments, the calculated CSP at 110±16 mm Hg, the pulse pressure between 45 and 50 mm Hg, and the frequency of pulsation at 2.5–3 Hz.

Baroreceptor responses with contralateral sinus intact or blocked and with and without halothane anaesthesia

Figure 2 presents a representative study showing NAP from the haemodynamically isolated carotid sinus when the contralateral sinus was intact (left panel) and blocked with 1% lignocaine 2–3 ml (right panel). As can be seen, there was a marked increase in the NAP following blockade of

TABLE I. *Systemic arterial pressure before and after blockade of contralateral carotid sinus nerve with 1% lignocaine 2–3 ml during the administration of different concentrations of halothane*

Halothane concn (%)	Systemic arterial pressure (mm Hg) Before blockade	Systemic arterial pressure (mm Hg) After blockade
0.0	115±15	122±20
0.5	100±12	105±10
1.0	85±8	86±7
1.5	78±9	77±8
2.0	55±7	56±6

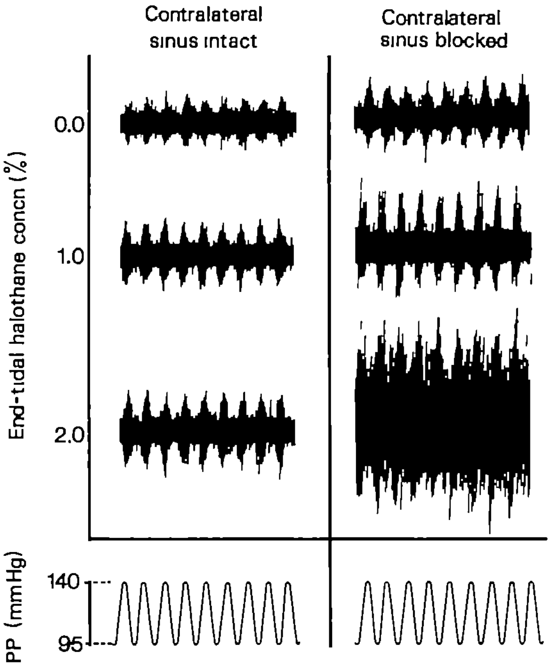

FIG. 2. A representative study showing the intrasinus pulsatile pressure and NAP from haemodynamically isolated carotid sinus with the contralateral sinus intact (left panel), and blocked with 1% lignocaine 2–3 ml (right panel). Note the marked increase in the NAP following blockade of the contralateral sinus in the absence of halothane and after 1 and 2% halothane administration.

the contralateral sinus in the absence of halothane and after administration of 1 and 2% halothane.

Effect of halothane on NAP with the contralateral sinus intact and blocked

Figure 3 (lower curve) shows a plot of the normalized nerve activity as a function of the percent end-tidal halothane concentration for dogs with the contralateral carotid sinus intact. There was a dose-dependent reduction in the NAP when the halothane concentration was increased from 0.0 to 1.0%. However, as the halothane concentration exceeded 1.0%, nerve activity increased. Thus our data reveal that the halothane effect on baroreceptor function exhibits a biphasic pattern, a finding similar to our previous observation (Behnia and Koushanpour, 1984).

Figure 3 (upper curve) shows a plot of normalized nerve activity as a function of percent end-tidal halothane concentration when the contralateral carotid sinus was blocked with lignocaine. Table II shows two-way analyses of variance between carotid sinus nerve action potentials, when NAP was significantly ($P < 0.001$) increased following blockade of the contralateral carotid sinus.

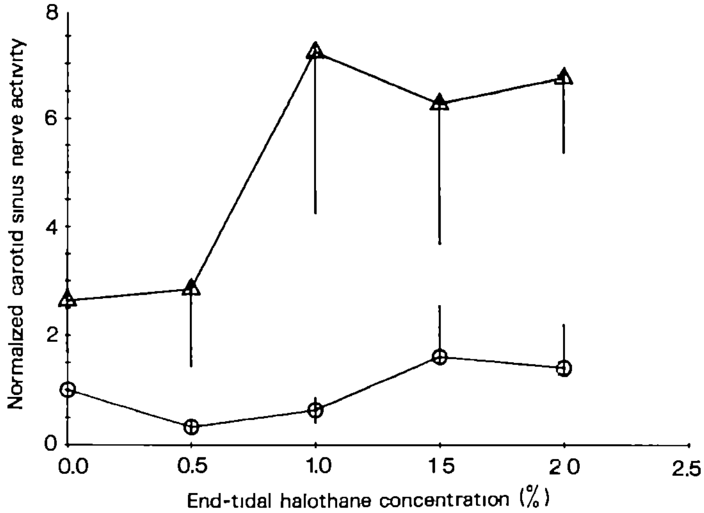

FIG. 3. Relationship between the normalized carotid sinus nerve activity as a function of end-tidal halothane concentration with contralateral sinus intact (○) and blocked with 1% lignocaine 2–3 ml (△).

TABLE II. *Two-way analysis of variance between two sets of carotid sinus nerve action potentials (NAP) recorded from the ipsilateral carotid sinus with the contralateral carotid sinus nerve either intact or blocked (with 1% lignocaine 2–3 ml). SS = Sum of squares; d.f. = degree of freedom; MS = mean of squares;* F = F-*ratio*

Source	SS	d.f.	MS	*F*	*P*
NAP (between groups)	238.52	1	238.52	20.13	< 0.001
Halothane effect	44.72	3	14.91	1.26	0.301
Interaction between halothane and NAP	24.81	3	8.23	0.70	
Within error	462.16	39	11.85		

DISCUSSION

In a previous study (Behnia and Koushanpour, 1984), we reported that halothane had no direct detectable local effect on the carotid sinus receptors and that its central inhibition produced a biphasic pattern on the NAP. In the present study, similar dose-dependent effects of halothane on the NAP were observed in an isolated carotid sinus model perfused with an artificial medium. Using a servo-controlled pressure generator, we perfused the haemodynamically isolated ipsilateral carotid sinus with oxygenated lactated Ringer's solution while the brain and other organs were perfused with blood containing halothane. The NAP from the ipsilateral carotid sinus nerve was recorded and quantitated with and without halothane anaesthesia while the contralateral sinus was either intact or blocked.

In the present study, the effects of the contralateral chemoreceptor, cervical sympathetic, aortic baroreceptor, and vagal influences on the overall baroreceptor reflex were eliminated by the blockade of the contralateral carotid sinus region. Specifically, the chemoreceptor effect was minimized by ventilating the dogs with 100% oxygen, and perfusing the isolated carotid sinus with oxygenated lactated Ringer's solution. This pulsatile perfusion system activated a group of fibres that fired in a pulse phasic pattern characteristic of arterial baroreceptors and eliminated chemoreceptor activity in the recorded NAP. We feel that, with these experimental manoeuvres, the contribution of the chemoreceptors in the measured NAP was minimal before and after the blockade of the contralateral carotid sinus. However, the influence of the ipsilateral aortic baroreceptor and vagus nerve could not be ruled out in this study. We did not block the ipsilateral aortic and vagus nerves because we were concerned that the lignocaine might diffuse to the cervical sympathetic nerves and the experimental sinus nerve, and result in complete loss of the nerve signal. A study by Ishikawa and Sagawa (1983) has shown that the depressor effect of the aortic nerve is greater between 80 and 90 mm Hg (physiological range) than in the sub- or supraphysiological range. In addition, these investigators have shown that simultaneous or separate stimulation of left or right aortic nerve produced a simple additive summation. On the basis of this report, it is reasonable to assume that blockade of the contralateral aortic nerve along with the carotid sinus nerve would not affect the ipsilateral aortic nerve or change its overall effect on the ipsilateral carotid sinus NAP measured during the course of this study. However, further studies are needed to define the separate influence of the aortic and vagus nerves on carotid sinus baroreceptor function.

As depicted in figure 3, and similar to our previous cross circulation study (Behnia and Koushanpour, 1984), halothane produced a dose-dependent biphasic effect on the NAP when the contralateral sinus was intact. Since the artificial medium used to perfuse the carotid sinus contained no halothane, the observed biphasic effect of halothane on NAP in this study could be attributed to its central modification of the baroreceptor function. It appears that halothane in concentrations of around 1% has a depressant effect on NAP.

Blockade of the contralateral carotid sinus nerve with 1% lignocaine 2–3 ml significantly ($P < 0.001$) increased ipsilateral NAP, suggesting an integrated communication between the two carotid sinuses. Blockade of the contralateral sinus separated the relative contribution of the contralateral sinus from those of central pathways in the observed effect of halothane. It is reasonable to assume that the elimination of the activity in the contralateral carotid sinus nerve altered central sympathetic outflow, thereby altering the sensitivity of the ipsilateral baroreceptor. However, since there was far more variability at 1.5 and 2% halothane than at 0.5 and 1%, interpretation of the excess enhancement of NAP at higher concentrations of halothane is difficult and its significance is uncertain at this time.

The observed biphasic response with the contralateral carotid sinus nerve intact may be explained as follows. Halothane anaesthesia caused a progressive dose-dependent systemic hypotension which led to a reduction in cerebral perfusion pressure and contralateral carotid sinus pressure. At low inspired concentrations (0.5–1.0%), halothane depressed the vasomotor centre, thereby reducing sympathetic efferent activity to the carotid sinus. However, progressive systemic hypotension produced by higher concentrations of halothane (1.0% and more), led to a reduction in the contralateral carotid sinus pressure and, thereby, increased sympathetic activity in the ipsilateral NAP, which was pump perfused at a constant pulsatile intrasinus pressure. This interaction between the function of the two carotid sinuses is consistent with a parallel integrated servo-controlled hypothesis proposed to explain the ability of mammals to maintain constant arterial pressure (Korner, 1971; Kirchheim, 1976). Our finding is also in agreement with the report of Felder, Heesch and Thames (1983) who showed an increase in the ipsilateral NAP when contralateral carotid sinus pressure was reduced by common carotid artery clamping.

Alternatively, it may be postulated that halothane, at higher concentrations, preferentially inhibits those central areas which have an inhibitory role in the baroreceptor feedback loop, leading to further increases in NAP. The existence of such a mechanism has been suggested by two studies (Majcherczycet et al., 1980; Koushanpour and Behnia, 1982).

In conclusion, the present study represents a first attempt to partition quantitatively the effect of halothane on the baroreceptor reflex with the contralateral sinus intact or blocked. Our finding is consistent with the hypothesis that modification of the baroreceptor reflex by halothane is mediated through its action at multiple sites along the integrated servo-controlled physiological pathway. More quantitative studies are needed to determine the selective functions of the peripheral and central baroreceptors during the resetting of arterial pressure under general anaesthesia. Extra- and intracellular recordings of neurones that mediate the central baroreceptor function would be a desirable technique to answer some of the questions raised in this study.

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Br. J. Anaesth. (1987), 59, 498–502

PROPHYLACTIC EFFECT OF AMINOPHYLLINE AND SALBUTAMOL ON HISTAMINE-INDUCED BRONCHOCONSTRICTION

J. G. JONES, C. JORDAN, B. SLAVIN AND J. R. LEHANE

SUMMARY

The effect of salbutamol 200 µg aerosol, i.v. high-dose aminophylline 670 mg or placebo (aerosol and infusion) on bronchomotor tone were compared in normal volunteers before and after bronchial provocation with histamine aerosol 500 µg. The study was a double-blind cross-over design. Specific airways conductance of the lower airway ($s.G_{law}$) was measured using a forced airflow oscillation technique. All subjects receiving aminophylline had tremor and irritability, whereas after salbutamol there were no noticeable systemic or psychological effects. Before the administration of histamine, salbutamol caused significant bronchodilatation compared with control: aminophylline did not induce a significant change in airway conductance. The effect of histamine administration on $s.G_{law}$ was only partially blocked by the high dose of aminophylline, but was completely blocked by salbutamol.

There is increasing awareness of the problem posed by adverse tissue reactions induced by general anaesthetic drugs (Lorenz and Doenicke, 1985a). An increase in plasma histamine concentration has been demonstrated in patients following the administration of thiopentone or methohexitone (Lorenz and Doenicke, 1985b), and thiopentone (but not methohexitone) released histamine from mast cells in human skin (Hirshman et al., 1985). Other workers report histamine release following the administration of narcotics and myoneural blocking drugs in man (Moss and Rosow, 1983). Doses of tubocurarine and atracurium, well within the clinical range, have been shown to produce large increases in bronchomotor tone in patients during anaesthesia (Simpson, Wright and Hammond, 1985). The latter workers assumed that the release of histamine was the most likely explanation, although other mediators could be involved. The increased sensitivity of asthmatics to exogenous histamine is well established (Cockcroft et al., 1977) although H_1- and H_2-type histamine antagonists are of no value in the management of asthma. In the context of bronchoconstriction induced by anaesthetic drugs, the release of histamine is likely to be only one component of a complex tissue reaction involving many different processes and other mediators and mechanisms are likely to be involved (Barnes, 1986).

Until the nature of these reactions is elucidated traditional bronchodilators will continue to be used in the management of bronchospasm occurring during anaesthesia. In clinical practice the i.v. administration of aminophylline is often the first line treatment of bronchospasm developing during anaesthesia.

The purpose of this study was to examine the relative effects of the β-agonist, salbutamol, and aminophylline on bronchomotor tone in normal subjects, and to study the prophylactic effect of either drug in ameliorating the bronchoconstrictor effect of exogenous histamine.

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PATIENTS AND METHODS

The study was approved by the Northwick Park Hospital Ethical Committee. We studied the effects of salbutamol, aminophylline and histamine on the specific conductance of the lower airway ($s.G_{law}$) in eight normal volunteers. Each subject was studied on three separate occasions, the subject lying in the supine position for each study period. The measurements of $s.G_{law}$ were made using the technique previously described (Jordan et al., 1981). In outline, this technique uses a forced airflow oscillation 55 ml at 3 Hz, using a sinusoidal pump driving a bronze bellows. The subject exhales slowly (approx. 75 ml s^{-1}) through a pneumotachograph connected to the sinusoidal flow. The total lung resistance (R_{rs}) is calculated at every cycle of the pump to obtain a curve of R_{rs} *v.* change in lung volume (V_L). An Apple II microcomputer is used to analyse the curve at the end of each manoeuvre and to fit a hyperbola to these data. The non-lung volume dependent resistance of the upper airway and chest wall (R_A) is derived from the horizontal asymptote of the resistance–volume curve and R_A is continuously subtracted from R_{rs} to give $1/(R_{rs} - R_A)$—the conductance of the lower airway (G_{law}). The plot of conductance against V_L is invariably linear and the slope ($s.G_{law}$) is used as an index of bronchomotor tone.

After measurements of baseline values of $s.G_{law}$ each subject received i.v. aminophylline, salbutamol aerosol or placebo in a randomized double-blind crossover fashion, every subject having an i.v. infusion of saline to which either aminophylline or placebo was added. To conceal the nature of the aerosol, we used either a conventional salbutamol metered-dose aerosol or an exactly similar container delivering only the propellant. Thus for two study days the subjects would receive i.v. dose aminophylline with placebo aerosol or salbutamol aerosol with placebo infusion. On the third occasion they would receive placebo by aerosol and infusion.

Further measurements of $s.G_{law}$ were made at 15, 25, 35 and 40 min following the administration of drug/placebo, then at 45 min histamine 50 µg was administered from a metered-dose cannister (Supplied by Riker Laboratories, Loughborough). These delivered 125 µg per puff inhaled in the standard fashion. Measurements of $s.G_{law}$ were repeated at 10-min intervals after the administration of the histamine while the infusion continued.

The doses of drug used were as follows: aminophylline 600 mg in 20 min followed by 1 mg min^{-1} for a further 70 min; salbutamol 200 µg aerosol. The aminophylline regimen was chosen on the basis of computer predictions based on the dose optimization (OPT) routine described by Kelman, Whiting and Bryson (1982).

Plasma theophylline concentrations were measured using the AMES TDA fluorescent immunoassay test (Miles Laboratories Inc. P.O. Box 70, Elkhart, Indiana, USA).

Statistical analysis

Logarithmic transformation was applied to the $s.G_{law}$ data to correct the positive skew in distribution. This also corrected for the association between the value of $s.G_{law}$ and degree of change observed (Jordan et al., 1981). Analysis of variance allowing for repeated measures (Winer, 1971) was applied to the logarithmic data.

RESULTS

Bronchomotor tone before histamine

The mean $s.G_{law}$ values (± SEM) after aminophylline are shown in figure 1 and were slightly greater than placebo, but this did not reach statistical signficance when the whole period before histamine was analysed. Salbutamol pro-

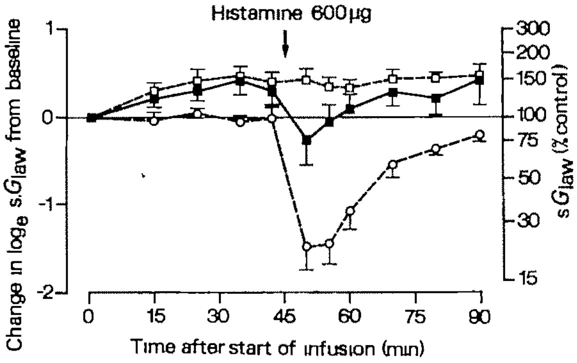

FIG. 1. Changes in specific conductance of the lower airway ($s.G_{law}$) following salbutamol (□), and aminophylline (■) compared with placebo (○). The time of administration of a histamine aerosol is shown. Before histamine there was a non-significant change in $s.G_{law}$ with aminophylline. $s.G_{law}$ following salbutamol was significiantly ($P < 0.05$) greater than placebo. Immediately after histamine there was no change in $s.G_{law}$ in the salbutamol group. The $s.G_{law}$ was significantly greater than placebo in the salbutamol ($P < 0.005$) and aminophylline ($P < 0.01$) groups, although $s.G_{law}$ in the aminophylline group was significantly less ($P < 0.05$) than in the salbutamol group.

duced a significantly larger ($P < 0.05$) s.G_{law} than did placebo. There were no significant trends with time.

Bronchomotor tone after histamine

Histamine produced a large increase in bronchomotor tone (decrease in s.G_{law}) on the placebo day (fig. 1). Salbutamol completely blocked any change in s.G_{law} following histamine administration (figs 1, 2) whereas aminophylline only partly blocked the histamine effect, there being a significant ($P < 0.05$) decrease in s.G_{law} compared with the salbutamol group. A typical set of curves of resistance and conductance in one of the subjects is shown in figure 2. There was no significant change in s.G_{law} following histamine in the salbutamol group. The s.G_{law} values following salbutamol and histamine were significantly different from placebo ($P < 0.005$). s.G_{law} following aminophylline was also significantly greater than placebo ($P < 0.01$).

Plasma theophylline concentrations were measured 40 min after the start of administration of aminophylline/placebo. Theophylline blood concentrations ranged from 13.6 to 19.2 µg ml^{-1} (mean 16.4 µg ml^{-1}). All subjects receiving the high dose aminophylline had tremor and marked irritability whereas no abnormalities were reported following salbutamol.

DISCUSSION

Many studies of the effects of bronchoactive drugs used conventional spirometry which has major drawbacks which complicate the interpretation of the relatively small effects of drugs on the airways. Maximal expiratory flow is determined by a complex interaction between the patency and compliance of the airways (Jones, Fraser and Nadel, 1975). For example, there may be no change in expiratory flow if a drug which promotes dilatation of airways, and an increase in flow, at the same time increases the compliance of the downstream airways causing a decrease in flow. Although some of these objections may be overcome by whole body plethysmography, we have used a technique that may be used in awake or anaesthetized patients and which measures the specific conductance of the intrathoracic (lower) airways (Lehane, Jordan and Jones, 1980; Jordan et al., 1981; Simpson, Wright and Hammond, 1985). The technique has an advantage over the body plethysmograph method in excluding the in-series resistance of the upper airway and, therefore, gives a more direct measurement of the effects of drugs on bronchomotor tone.

Using this technique we found that aminophylline had no significant effect on resting bronchomotor tone compared with placebo.

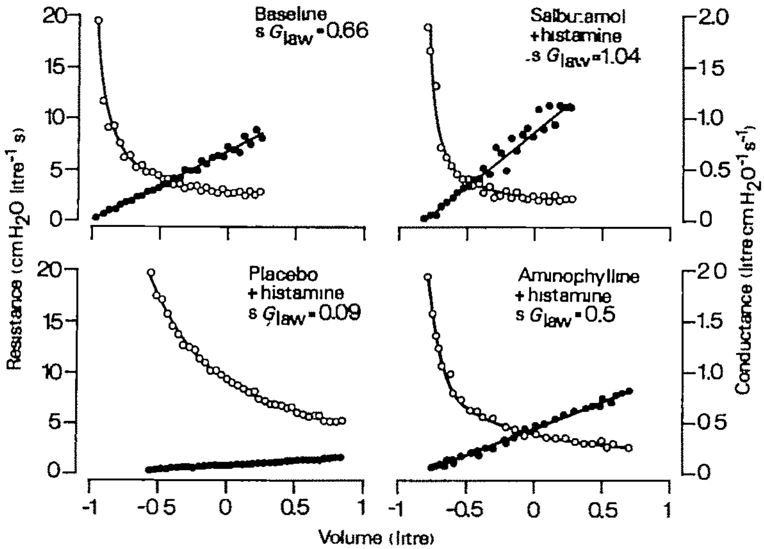

FIG. 2. Data from one subject to show changes in airway resistance (○) and conductance (●) plotted against change in lung volume. This shows the effect of salbutamol, placebo and aminophylline on the response to histamine.

Nevertheless, this dose of aminophylline did cause partial protection from histamine-induced bronchoconstriction. In contrast, salbutamol produced both bronchodilatation and complete blockade of the constrictor effect of histamine on the airways. The lack of complete protective effect against histamine, even at high doses of aminophylline with the attendant unpleasant side effects, implies that this drug is a less effective bronchodilator than salbutamol.

These changes with aminophylline are similar to those reported by Estenne, Yernault and de Troyer (1980) who showed a lack of bronchodilatation measured by the body plethysmograph at theophylline blood concentrations between 15 and 19 μg ml^{-1}. In fact, their data showed a small increase in resistance, but no indication was given if this change was significant.

The administration of β_2-adrenoreceptor agonists or muscarinic cholinergic antagonists produce bronchodilatation in normal man. Relaxation of bronchomotor tone by β_2-agonists is thought to be the result of increased smooth muscle concentrations of 3′5′-cyclic adenosine monophosphate (cyclic AMP) and uncoupling of excitation–contraction mechanisms. However, there is evidence that aminophylline does not produce bronchodilatation in normal subjects (Estenne, Yernault and de Troyer, 1980; Payne, Chester and Hsi, 1967), despite the fact that this drug increases cyclic AMP although, at blood concentrations of 10–20 μg ml^{-1}, there is little effect of aminophylline on phosphodiesterase. In contrast, aminophylline is a bronchodilator in patients with asthma, although it is not established whether it can achieve the same degree of bronchodilatation as that produced by β_2-agonist drugs.

It has been suggested that the cellular actions of methylxanthines are those (a) associated with translocations of intracellular calcium; (b) mediated by increased cyclic nucleotides attributable to phosphodiesterase (PDE) inhibition; (c) mediated by blockade of adenosine activity; (d) of inhibition of eicosanoid synthesis and (e) associated with a reduction in catecholamine uptake or metabolism (Gilman, Goodman and Gilman, 1980). The tolerable concentrations of theophylline are such as to exclude (a) and Cushley, Tattersfield and Holgate (1984) have argued convincingly against any possible effect of theophyllines on PDE inhibition as a cause of bronchodilatation. The leading contender for the latter effect appears to be the inhibition by theophyllines of adenosine-induced bronchoconstriction. Adenosine causes bronchoconstriction in asthmatic subjects (Cushley, Tattersfield and Holgate, 1984) but no change in normal individuals. However, Satchell and Smith (1984) report that adenosine causes contractions in spiral strips, but relaxation of transverse strips of guineapig trachea. Both of these opposing effects were reversed by theophylline, suggesting that both responses are mediated by a purinergic (P_1) receptor (Burnstock, 1978). The contractile response to adenosine could be antagonized by hyoscine, which suggested that adenosine could act by releasing acetylcholine. However, in man, adenosine-induced bronchoconstriction in asthma is not blocked by ipratropium bromide despite displacement of the methacholine dose–response curve to the right (Holgate, personal communication).

The lack of effect of adenosine on bronchomotor tone in the normal lung is suggested by the possibility that the constricting and relaxing effects are normally in balance. A slight imbalance of these effects would give rise to either a constrictor or a dilator effect of adenosine and, thus, aminophylline. If a small constrictor effect is normally dominant, then the administration of aminophylline, by antagonizing this effect, could lead to bronchoconstriction which, although too small to demonstrate in clinical studies, may protect against the effects of the administration of histamine which may also exert a bronchoconstrictor effect by the release of adenosine (Bockman, Berne and Rubio, 1975; Marquardt, Parker and Sullivan, 1978).

There was a clear advantage of salbutamol compared with aminophylline in completely blocking histamine-induced bronchoconstriction. This was achieved in the absence of any noticeable side effects. A comparable improvement in specific airway conductance using the body plethysmograph method has been shown in asthmatics given either the β_2-agonist terbutaline or aminophylline (Wolfe et al., 1978). Others (Barclay et al., 1981) have shown that, in patients with chronic bronchitis, a maximum bronchodilatation response to theophylline could be achieved and the subsequent administration of salbutamol induced further dilatation. Furthermore, Passamonte and Martinez (1984) showed that, in patients with chronic obstructive lung disease stabilized on high doses of theophylline, the further administration of β-agonists and atropine produced further bronchodilatation.

These results suggest that salbutamol, given prophylactically, is more efficacious in blocking the effects of histamine in the airways than is aminophylline. Consideration should be given to the prophylactic administration of this drug in patients with a previous history of histamine-like reactions during anaesthesia.

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Br. J. Anaesth. (1987), 59, 503–509

COMPARISON OF THE LEICESTER MICROPALLIATOR AND THE CARDIFF PALLIATOR IN THE RELIEF OF POSTOPERATIVE PAIN

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SUMMARY

Two devices for providing patient-controlled, on-demand analgesia were compared for 24 h after abdominal surgery. The Leicester Micropalliator delivered a mandatory background infusion of 1 mg h^{-1} in addition to on demand bolus doses of morphine 2 mg i.v. while the Cardiff Palliator provided only bolus doses of morphine 2 mg i.v. The Leicester Micropalliator provided analgesia superior or equivalent to that of the Cardiff Palliator in patients who had undergone hysterectomy or cholecystectomy, respectively, and there was no increase in side effects. The total doses of morphine administered over 24 h did not differ significantly between the two devices.

Patient controlled analgesia (PCA) is a technique whereby patients self administer small bolus closes of opioids i.v., and has been shown to be of value in the relief of postoperative pain (Ellis et al., 1982; Welchew, 1983). Currently, there are several items of apparatus available commercially, including the Cardiff Palliator and the Janssen on-demand analgesic computer. The main difference between these is that the former permits the delivery of a preset bolus of drug, whilst the latter provides in addition, a low dose i.v. infusion. In theory, the latter strategy should permit superior analgesia (Hull, 1985). Both devices are relatively bulky and expensive.

The Leicester Micropalliator is a device which provides both bolus doses and a continuous background infusion, and was developed in an attempt to improve on existing PCA apparatus. The Micropalliator has been described elsewhere (Burt et al., 1985). In summary, it comprises a commercially-available Graseby Dynamics MS16 syringe driver controlled by a microprocessor developed by the Medical Physics Department at the Leicester Royal Infirmary. The control unit has two main components: a central processing unit (CPU) and a programmable memory (EPROM), both utilizing commonly available microchips. It is able to control the background infusion rate, detect and acknowledge patient requests, supply the appropriate bolus dose and display the number of doses already delivered. In addition, it monitors input from the syringe driver and is, thus, capable of detecting faults within the system. In the event of a malfunction it generates an audible signal and remains in the inactive state. The Micropalliator is inexpensive, light, battery-powered and easily carried in a holster hanging from the patient's shoulder (Burt et al., 1985).

The object of the present study was to compare the Leicester Micropalliator with the Cardiff Palliator in terms of quality of analgesia and frequency of side-effects, and to assess whether the portability of the Leicester machine offered practical advantages in the management of pain in the postoperative period.

PATIENTS AND METHODS

Female patients (ASA Grades I or II) who were to undergo elective cholecystectomy or hysterectomy gave informed consent to the study, which was

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approved by the District Ethical Committee. In each group, patients were assigned randomly to receive postoperative analgesia with either the Cardiff Palliator or the Leicester Micropalliator.

For the purpose of this study, the Leicester Micropalliator was preset to deliver a 2-mg bolus dose of morphine with a "lock-out" time of 10 min; that is, the machine remained inactive for 10 min after delivering a bolus. The constant mandatory background infusion of morphine was set at a dose of 1 mg h^{-1}. The Cardiff Palliator used in this study was also set to deliver a 2-mg bolus dose of morphine with a lock-out time of 10 min. Both devices were attached to pen recorders to monitor the delivery of opioid.

At the preoperative interview, the patient's height and weight were recorded, as was the optimum value of three assessments of the peak expiratory flow rate (PEFR) using a Wright peak flow meter. The operation of the appropriate device was explained and demonstrated to each patient.

All patients received a standard anaesthetic technique consisting of diazepam 10 mg by mouth as premedication, thiopentone 3–4 mg kg^{-1}, neuromuscular blockade, and 67% nitrous oxide with 33% oxygen supplemented with morphine 10 mg i.v. Halothane was administered to supplement anaesthesia if deemed necessary according to the clinical judgement of the anaesthetist. In the immediate postoperative period, an i.v. dose of morphine was administered if considered necessary. The total dose of morphine administered during, and immediately after, surgery was recorded as the perioperative dose. On return to the ward, each patient was provided with the appropriate palliator. The study was conducted over the first 24 h after surgery, although the patients were able to continue to use the palliator for longer if they wished.

The total cumulative dose of morphine (including the perioperative dose) was recorded at 6-hourly intervals for 24 h. At 20 h after institution of demand analgesia, the patients were assessed at 30-min intervals for 4 h using measurement of PEFR and visual analogue scores (VAS) for pain, nausea, sedation and dizziness. The scores for nausea, dizziness and sedation were combined to produce a total side-effects score. At 24 h the patients were asked to assess average and maximum pain experienced during the trial period using a visual analogue scale, and to give their subjective views on the particular palliator used.

Data were analysed using the Wilcoxon Rank Sum Test for comparisons of VAS and unpaired Student's t tests were applied to all other data. A value of $P < 0.05$ was used as an index of statistical significance.

RESULTS

The groups were comparable in terms of age, weight, height and preoperative PEFR, and the number of patients undergoing cholecystectomy or hysterectomy (table I).

The patients undergoing cholecystectomy exhibited no significant differences between the two palliator groups in terms of total cumulative morphine dose (over the first postoperative 24 h) (fig. 1), VAS for pain (fig. 2), nausea (fig. 3) or combined side effects (nausea, sedation and dizziness) (fig. 4). The decrease in PEFR as a percentage of preoperative values (fig. 5) was not significantly different between the two groups and VAS for average and maximum pain were not significantly different between groups, although there was a very wide scatter of results (table II).

In the patients undergoing hysterectomy there were significantly lower pain scores in the Leicester Micropalliator group at 20 h ($P < 0.05$), 22 h ($P < 0.05$) and 24 h ($P < 0.01$) after the institution of PCA (fig. 6). However, there were

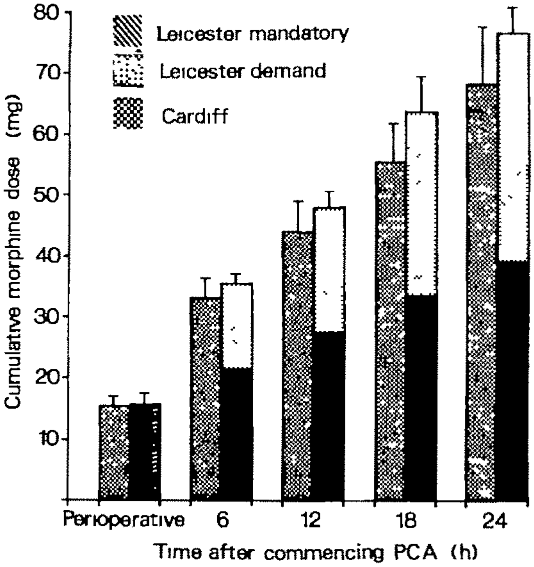

FIG. 1. Total cumulative dose of morphine during the perioperative period and for 24 h after commencing PCA for patients undergoing cholecystectomy (mean + SEM).

TABLE I. *Demographic data (mean values ± SEM)*

		n	Age (yr)	Height (m)	Weight (kg)	Preop. PEFR (litre min^{-1})
Cholecystectomy	Cardiff	10	37.3 (2.9)	1.61 (0.02)	61.1 (2.8)	397.5 (16.1)
	Leicester	10	40.0 (4.9)	1.63 (0.02)	60.6 (2.8)	399.0 (13.1)
Hysterectomy	Cardiff	10	44.0 (1.2)	1.65 (0.02)	63.8 (2.8)	397.5 (10.5)
	Leicester	10	41.5 (2.0)	1.62 (0.02)	67.0 (1.8)	410.0 (29.5)

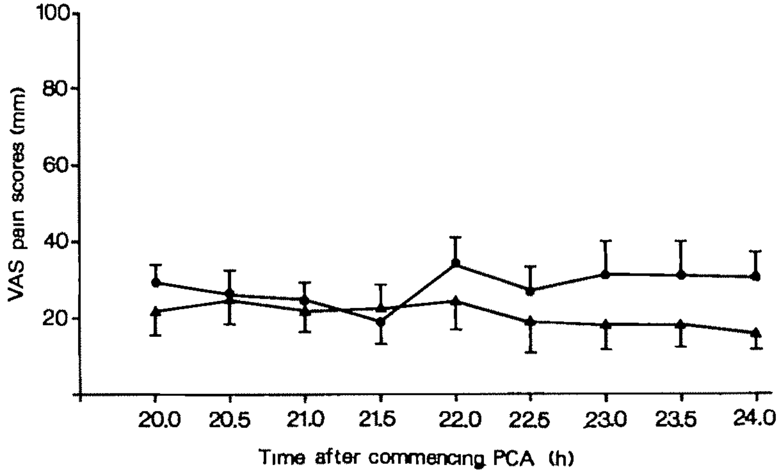

FIG. 2. Visual analogue scores for pain during 4-h assessment period in patients undergoing cholecystectomy (mean + SEM). ● = Cardiff; ▲ = Leicester.

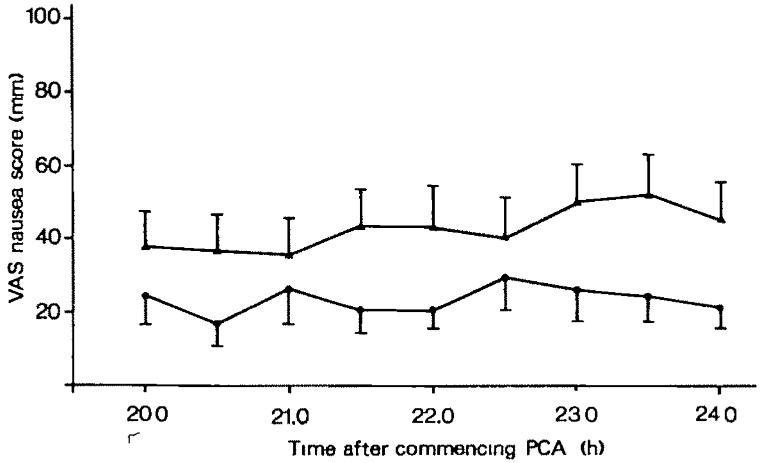

FIG. 3. Visual analogue scores for nausea during 4-h assessment period for patients undergoing cholecystectomy (mean + SEM). ● = Cardiff; ▲ = Leicester.

TABLE II. *Average and maximum visual analogue pain scores (mean ± SEM) 24 h after commencing PCA*

		Average pain	Maximum pain
Cholecystectomy	Cardiff	54.5 (5.5)	68.3 (7.4)
	Leicester	32.3 (5.6)	61.4 (4.5)
Hysterectomy	Cardiff	48.4 (6.7)	82.5 (7.4)
	Leicester	42.1 (6.3)	72.3 (7.2)

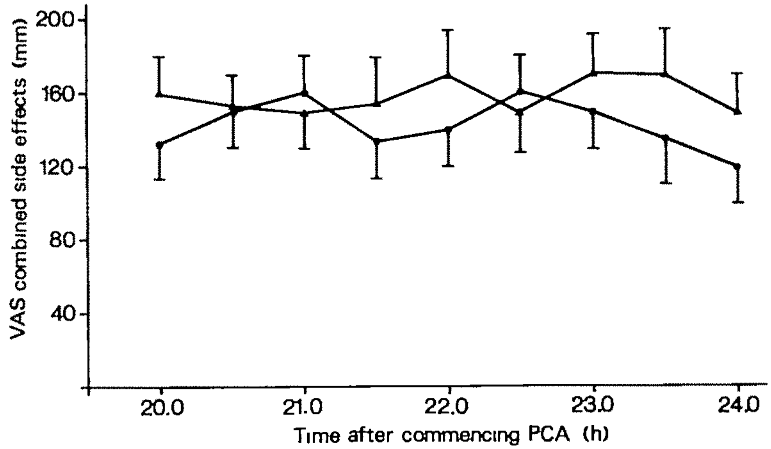

FIG. 4. Visual analogue scores for combined side effects (nausea, sedation and dizziness) during 4-h assessment period in patients undergoing cholecystectomy (mean + SEM). ● = Cardiff; ▲ = Leicester.

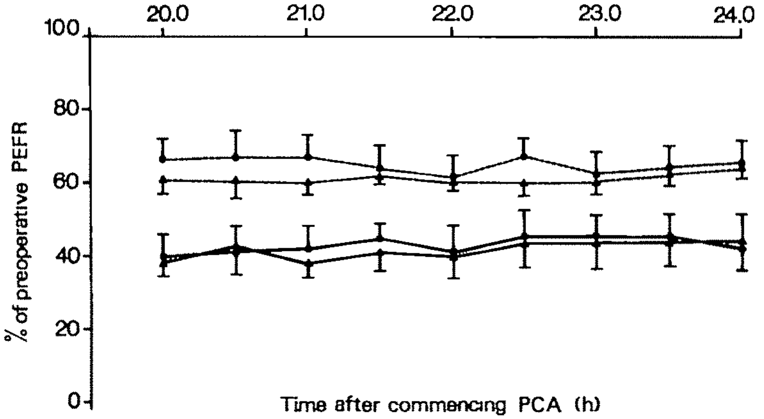

FIG 5. Decrease in PEFR as a percentage of preoperative value during 4-h assessment period (mean + SEM). ● = Cardiff; ▲ = Leicester. ×——× = Cholecystectomy; ×-----× = hysterectomy.

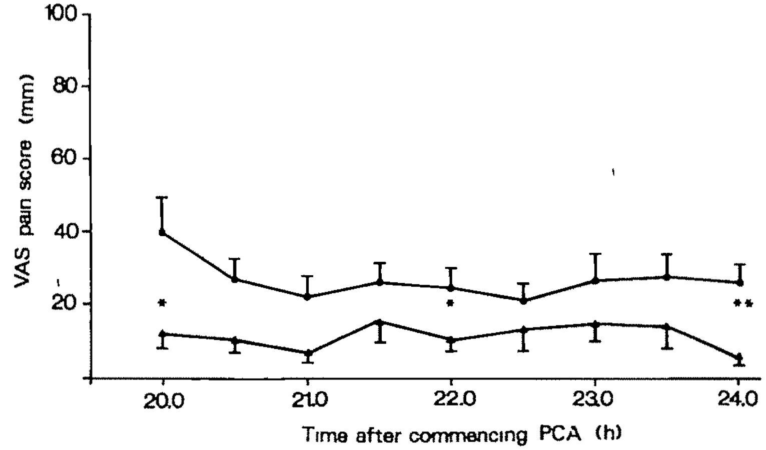

FIG. 6. Visual analogue scores for pain during 4-h assessment period in patients undergoing hysterectomy (mean + SEM). $^*P < 0.05$; $^{**}P < 0.01$. ● = Cardiff; ▲ = Leicester.

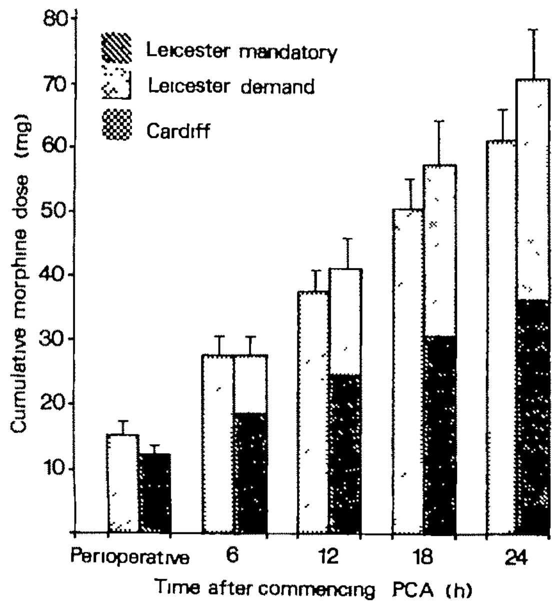

FIG. 7. Total cumulative morphine dose during the perioperative period and for 24 h after commencing PCA for patients undergoing hysterectomy (mean + SEM).

no significant differences between the two analgesic regimens with regard to total cumulative morphine administration (fig. 7), VAS for nausea (fig. 8), PEFR (fig. 5), and average and maximum pain scores (table II). Patients using the Leicester Micropalliator had significantly lower VAS for combined side effects (fig. 9) at 20 h after commencing PCA ($P < 0.05$).

All the patients expressed satisfaction with the analgesia provided and found the devices simple to use. Only one patient expressed any concern over the palliator used.

DISCUSSION

The results of this study show that comparable analgesia and side effects were achieved with the Leicester Micropalliator and the Cardiff Palliator when used to provide postoperative analgesia after cholecystectomy. After hysterectomy there was a small, but significantly better degree of analgesia with the Leicester Micropalliator than the Cardiff machine between 20 and 24 h after surgery.

In providing better analgesia in the hysterectomy group, the same total dose of morphine was administered by the Leicester Micropalliator as by the Cardiff Palliator even though morphine 24 mg was given by mandatory infusion during the study period by the former device in addition to the "on demand" bolus doses. The amount of analgesic required during PCA shows wide variation between individuals (Tamsen et al., 1979), and the doses received by all groups in this study were in the same range as those reported previously. Superior analgesia would be expected with the Leicester machine on theoretical grounds, since a low dose infusional strategy plus bolus doses would be accompanied by smaller fluctuations in the plasma concentrations of analgesic drug than a regimen relying only upon intermittent administration of i.v. bolus doses.

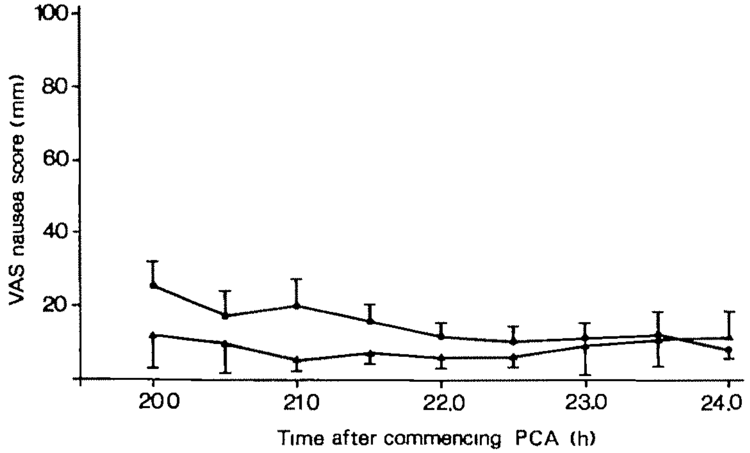

FIG. 8. Visual analogue scores for nausea during 4-h assessment period in patients undergoing hysterectomy (mean + SEM). ● = Cardiff; ▲ = Leicester.

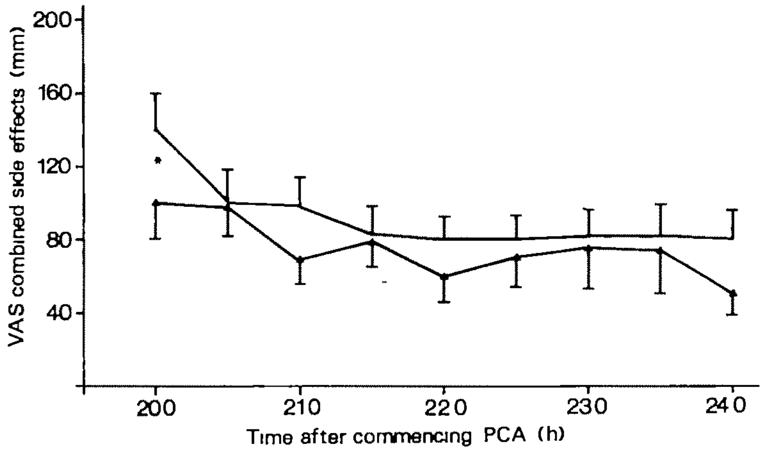

FIG. 9. Visual analogue scores for combined side effects (nausea, sedation and dizziness) during 4-h assessment period in patients undergoing hysterectomy (mean+SEM). $^*P < 0.05$. ● = Cardiff; ▲ = Leicester.

The evaluation of different techniques for providing analgesia is rendered difficult by the lack of reliable methods of quantifying pain. The use of visual analogue scales where the patient "scores" his pain on a 10-cm horizontal line has been shown to give reproducible results (Revill et al., 1976). In addition, the effect of surgery on PEFR, particularly after thoracic or upper abdominal surgery, has been shown to correlate well with VAS pain scores (Ellis et al., 1982). The selection of patients undergoing cholecystectomy or hysterectomy represents a severe test of any technique of postoperative analgesia, and it is noteworthy that in the present study there was little difference between the groups in respect of PEFR.

The use of on-demand analgesia as a means of measuring pain was first described by Sechzer in 1968. He observed a positive correlation between the degree of pain experienced and the amount of analgesic requested. Pursuing this observation, Forrest, Smethurst and Kienitz (1970) proposed that PCA might be used as a practical technique for the relief of pain. Subsequently, there have been many studies describing the use of PCA in the management of postoperative pain and comparing this technique with other methods. Keeri-Szanto, one of the pioneers of the practical use of PCA, commented on the inadequacy of analgesia resulting from i.m. pethidine and indicated that on-demand analgesia was associated[with "almost total pain relief" (Keeri-Szanto and Heamen, 1972). This was not confirmed by Ellis and colleagues (1982) who compared on-demand pethidine with morphine i.m. as required and sublingual buprenorphine and found no difference between these regimens in terms of analgesia. More recently. Welchew (1983), in a prospective double-blind trial, compared on-demand fentanyl with regular i.m. morphine and also found no difference in analgesia, while the incidence of nausea was less in the morphine group.

The Cardiff Palliator was the first commercially available PCA device and Evans and colleagues (1976) described its use in the relief of pain in labour. Chakravarti and colleagues (1979) used the final production model to demonstrate the efficacy of both pethidine and buprenorphine on an on-demand basis. All these studies showed that PCA produced good relief of acute pain. However, pain scores were rarely less than 20 mm as was found in the present study, suggesting that during PCA a balance is obtained between the analgesia and the side effects induced by the drug (Vickers, 1985).

PCA has also been compared with local anaesthetic techniques which might be expected to produce excellent postoperative analgesia. However, it is noteworthy that, when comparing extradural bupivacaine with i.v. fentanyl administered by Janssen demand analgesic computer in patients undergoing peripheral vascular surgery, White, Pearce and Norman (1979) found comparable pain relief. In that study, the Janssen machine was set to to deliver a constant infusion plus doses on demand.

The Leicester Micropalliator is capable of providing an infusion plus bolus doses and is small, portable and inexpensive. As far as the authors are aware, no previous studies have compared PCA by bolus plus infusion with bolus doses alone. The results confirm the theoretical premise that the former regimen offers better analgesia after hysterectomy, whilst comparable analgesia was produced after cholecystectomy. The improvement in analgesia in the hysterectomy group was not associated with an increase in side-effects. All the patients found that the Leicester Micropalliator was acceptable as a means of providing postoperative analgesia, although there did not appear to be advantages in the portability of this machine with the type of surgery studied. In conclusion, it should be noted that the results of our study cannot be extrapolated to the use of drugs with durations of action different from that of morphine.

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ASSESSMENT OF A HIGH FREQUENCY VENTILATOR BREATHING SYSTEM FOR USE IN THE OPERATING THEATRE

An Experimental and Clinical Study

K. M. SHERRY, S. WITHINGTON AND R. O. FENECK

SUMMARY

A breathing system capable of delivering positive pressure ventilation to the lungs at high frequencies and using anaesthetic gases and vapours is assessed. The recommended fresh gas flow at the ventilatory rates tested in this study was 100 ml kg^{-1}*. At 80 and 100 b.p.m. the system provided adequate ventilation, good oxygenation and haemodynamic stability. When compared with conventional positive pressure ventilation (CPPV), peak airway pressure (peak* P_{aw}*) was lower and mean airway pressure (*$P_{\overline{aw}}$*) was lower (80 b.p.m.) or unchanged (100 b.p.m.). There was some inherent positive end-expiratory pressure (PEEP) associated with the technique.*

There is a growing awareness of the benefits of high frequency ventilation (HFV), especially in patients at risk of lung damage from barotrauma. In addition, the potential advantages of the technique in microneurosurgery, and as a supplement to spontaneous ventilation have been reviewed (George and Geddes, 1985). However, equipment which would permit HFV in theatre using conventional anaesthetic gases and vapours is limited. Although a method has been described recently which enables conventional inhalation anaesthetics to be delivered to the patient's lungs at high rates of ventilation, this has utilized a purpose-built, and as yet, commercially unavailable ventilator (Whitwam et al., 1983.) We have developed an anaesthetic breathing system which can be used in the operating theatre in combination with a simple, commercially available high frequency ventilator. The system is valveless with a low resistance, and can deliver HFV to the lungs of the paralysed or spontaneously-breathing patient. It can be adapted to permit manual ventilation by inserting an open-tailed reservoir bag in place of the filter/muffler and can be easily cleaned since the system is made of metal and lightweight disposable plastic tubing. The system is illustrated in figure 1.

This study was designed to evaluate the ventilator system: (1) to determine the effect of changing resistance and compliance on tidal volumes during high frequency ventilation: (2) to determine the conditions under which only the anaesthetic gas and not the driving gas enters the lung: (3) to confirm that it is an appropriate means of providing adequate ventilation of the lungs at high frequencies, and (4) to assess the effect of this system on the airway pressures and haemodynamics of the patient.

PATIENTS AND METHODS

Materials and methods

Figure 1 shows the design of the ventilation breathing system used in this study. A high frequency ventilator (Accutronic VS 600), capable of delivering from 8 to 600 b.p.m. at pressures of up to 4 bar was used as a pneumatic piston on the expiratory limb of a T-piece. Oxygen was used as the driving gas and the dimensions of the tubing between the fresh gas inlet and the driving source

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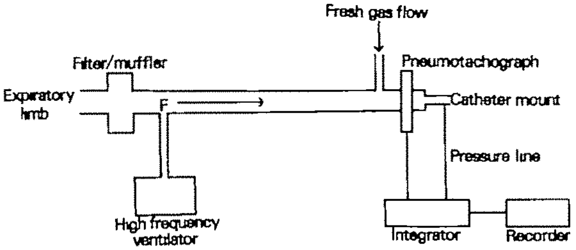

FIG 1. Diagram of the high frequency ventilator and T-piece system. F = injector nozzle.

were: internal diameter 22 mm, length 80 cm and volume 304 ml. Delivered gas volumes and flow rates were measured at the catheter mount by a pneumotachograph (Mercury Electronics VP5 Ventilator/Pump Test meter). This machine is described as having a response time of 4.2 Hz, and a rise time of 80 ms maximum. A transducer is incorporated to the unit permitting the simultaneous measurement of airway pressures. The calibration of the machine was verified repeatedly throughout the study against known pressures and volumes. The model lung used in this study complied with ISO standards and has been described elsewhere (Chakrabarti and Sykes, 1976).

Preliminary studies

Studies of the ventilator were undertaken using a model lung: first, to measure the changes in tidal volume at three values of compliance (0.05, 0.02 and 0.01 litre cm H_2O^{-1}) and three levels of resistance (5, 20, and 50 cm H_2O litre^{-1} s^{-1}) at frequencies between 40 and 200 b.p.m. At each setting, tidal volume was measured on a breath-to-breath basis and the mean of 20 breaths recorded. Second, to detect mixing of the fresh gas flow and driving gas. For this purpose 2% halothane was vaporized (Halothan Vapor 19.3 vaporizer, Dragerwerk A.G.) in oxygen and was delivered to the lung at flow rates of 4.9 litre min^{-1} and 7 litre min^{-1} (equivalent to 70 ml kg^{-1} min^{-1} and 100 ml kg^{-1} min^{-1} for a 70-kg man) and its concentration measured (Penlon halothane meter), at the output from the vaporizer and at the patient end of the circuit, for a similar range of ventilation rates and tidal volumes.

Patient studies

The clinical investigation was undertaken on three groups of 10 patients (total 30) who received HFV at either 80, 100 or 150 b.p.m. All patients had clinically normal lung function and were undergoing elective surgery involving cardiopulmonary bypass (NYHA 1 or 2). The study period was from the induction of anaesthesia until aortic cannulation. Patients were anaesthetized using a technique consisting of a benzodiazepine, an opioid and myoneural blockade. The trachea was intubated with a Mallinkrodt Hi-Lo Jet tracheal tube, and an internal jugular vein and a radial artery were cannulated. Intratracheal pressures were measured from the pressure-sensing lumen at the tip of the tracheal tube using a transducer (Mercury Electronics) calibrated against a mercury manometer. The electrocardiogram (standard lead II), and arterial and venous pressures were displayed (Roche monitors). Ventilation of the lungs was established using a Blease Manley ventilator set to deliver 100% oxygen at 100 ml kg^{-1} min^{-1} with a tidal volume of 10 ml kg^{-1}. Inspiratory pressures and flow rates were adjusted to give the minimum peak airway pressure before the baseline cardiovascular data and airway pressures were recorded. Patients were then transferred to the high frequency system set to deliver 100% oxygen to the lungs with an inspiratory time of 30% and a fresh gas flow of 100 ml kg^{-1} min^{-1}. The driving pressure was adjusted to maintain arterial carbon dioxide tensions (Pa_{CO_2}) between 4.0 and 5.5 kPa. If the Pa_{CO_2} increased to more than 6.0 kPa when the driving pressure was maximal the ventilation rate was decreased and subsequent readings excluded from analysis. Cardiovascular data, airway pressures, tidal volumes and driving pressures were recorded at 10, 20, 30 and 45 min following the start of high frequency ventilation or until aortic cannulation if this was sooner. At each of these times arterial blood was withdrawn for the measurement of arterial blood-gas tensions (ABL-3, Radiometer Ltd).

RESULTS

Preliminary studies

The results of altering the mechanics of the model lung are presented in figures 2, 3 and 4.

For the given ventilating frequencies and a driving pressure of 4 bar, the tidal volume decreased with increasing resistance and decreasing compliance. Pressures measured within the model lung (i.e. "alveolar" pressures) increased

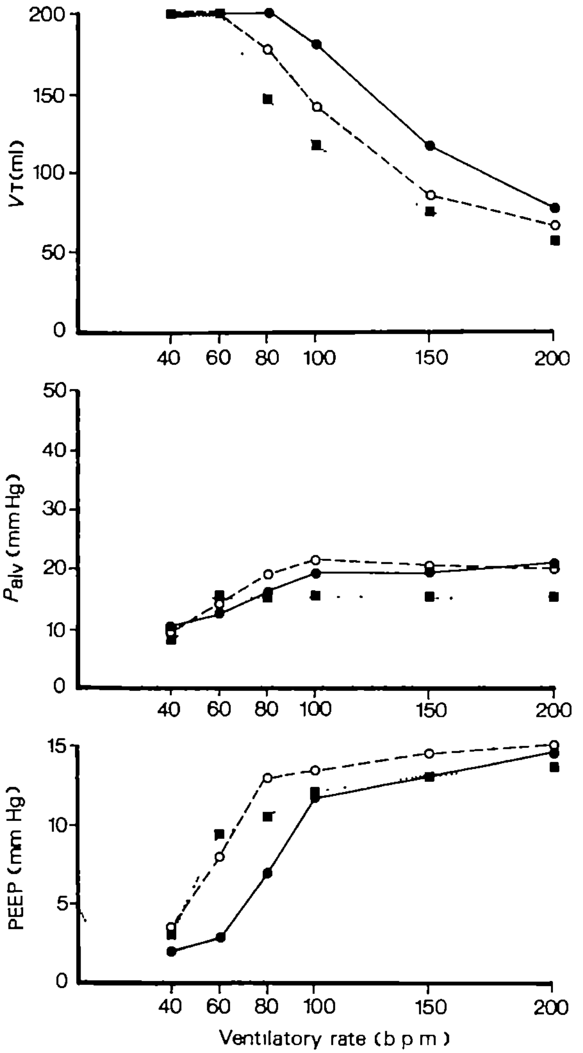

FIG. 2. The relationship between tidal volume (V_T), "alveolar" pressure (P_{alv}) and positive end-expiratory pressure (PEEP) at different ventilating frequencies. Lung compliance equals 0.05 litre cm H_2O^{-1}; resistance values (cm H_2O litre^{-1} s^{-1}) as follows: ●——● = 5, ○——○ = 20, ■——■ = 50.

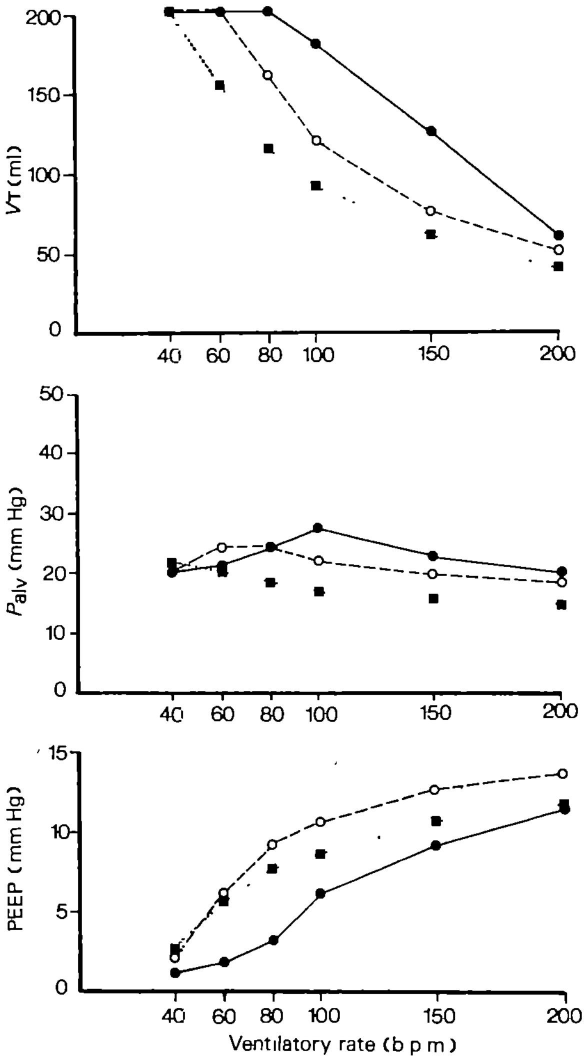

FIG. 3. The relationship between V_T, P_{alv} and PEEP at different ventilating frequencies. Lung compliance equals 0.02 litre cm H_2O^{-1}; resistance values (cm H_2O litre^{-1} s^{-1}) as follows: ●——● = 5, ○——○ = 20, ■-- ·■ = 50.

markedly with decreasing compliance, whereas positive end-expiratory pressure (PEEP) increased with increasing ventilatory frequency.

The halothane concentrations measured at the mouthpiece are shown in table I. Decreases in concentration, of greater than 0.1% halothane, were observed at a minute ventilation of 15 litre when the fresh gas flow was equivalent to 70 ml kg^{-1} min^{-1}, and at a minute ventilation of 22.5 litre when the fresh gas flow was equivalent to 100 ml kg^{-1} min^{-1}.

Patient studies

Results have been analysed by one-way analysis of variance for the changes on HFV with time, paired *t* tests for changes between CPPV and HFV and unpaired *t* tests for changes between the groups. A probability value of less than 5% was accepted as significant.

Tidal volumes and driving pressures. In each group, tidal volume decreased on changing to

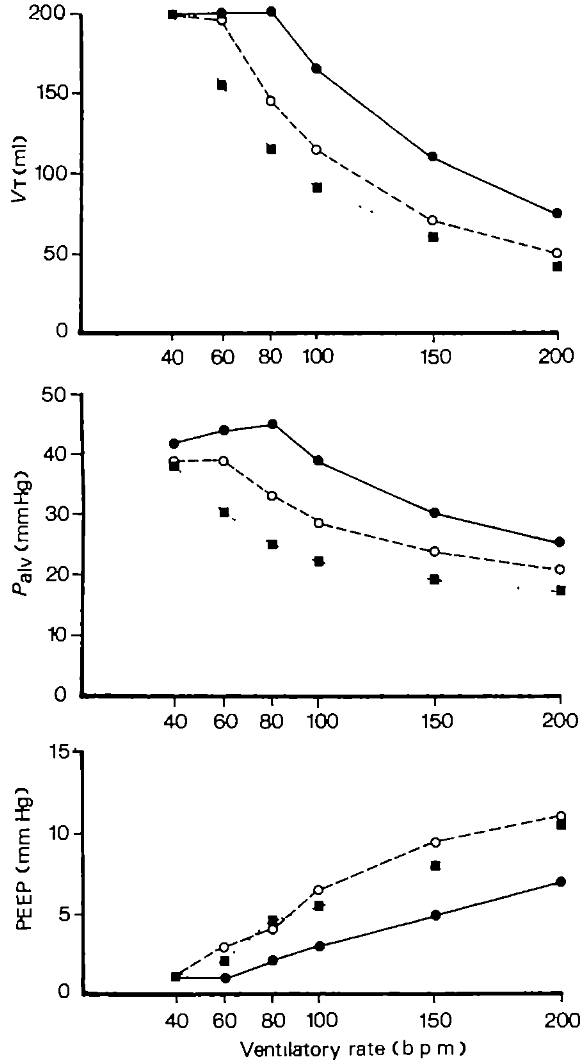

FIG. 4. The relationship between V_T, P_{alv} and PEEP at different ventilating frequencies. Lung compliance equals 0.01 litre cm H_2O^{-1}; resistance values (cm H_2O litre^{-1} s^{-1}) as follows: ●——● = 5, ○——○ = 20, ■-----■ = 50.

HFV and, thereafter, remained constant (table II). Tidal volume was significantly larger with HFV at slower rates. The driving pressures required to achieve these tidal volumes are shown in table II, and decreased progressively with decreasing rate. Two patients in group 1, seven patients in group 2 and all patients in group 3 received the maximum driving pressure of 4 bar.

Blood-gas tensions. There was no difference in the arterial oxygen tensions (Pa_{O_2}) on changing from conventional ventilation (CPPV) to HFV at any rate and no subsequent change with time (table III). There was no significant correlation in any group between mean airway pressure or end-expiratory pressure (PEEP) and Pa_{O_2} on HFV. Pa_{CO_2} increased on changing to HFV at 150 b.p.m. and continued to increase throughout the study period. In two patients in group 3 the Pa_{CO_2} reached 7 kPa, at which time the ventilating rate was decreased to 100 b.p.m. This resulted in an increase in tidal volume and the Pa_{CO_2} decreased to normal. In all patients ventilated at 80 and 100 b.p.m., normocarbia was maintained without alteration of the ventilation rate. There was no correlation between tidal volume and Pa_{CO_2} in any group.

TABLE I. *Halothane concentrations measured at the mouthpiece of the breathing system when 2% halothane is delivered in the fresh gas flow at the stated ventilating rates and minute ventilation*

Ventilation rate (b.p.m.)	Minute volume (litre)	Halothane concn (%)	
		4.9 litre min^{-1}	7.0 litre min^{-1}
60	9	1.9	2.0
80	12	1.9	2.0
100	15	1.9	1.95
150	22.5	1.75	1.9
200	26	1.35	1.7
250	22.5	1.55	1.8

Airway pressures. Peak airway pressures (peak P_{aw}) decreased in all groups on changing to HFV and, thereafter, remained stable, especially in groups 2 and 3 (table IV). The decreases in peak P_{aw} were 14% in group 1, 17% in group 2 and 34.5% in group 3. There was no overall difference in peak P_{aw} between the groups. On changing from CPPV to HFV, the mean airway pressure ($P_{\overline{aw}}$) decreased in group 1. However, there were no significant decreases in groups 2 and 3. $P_{\overline{aw}}$ was significantly lower with slower rates of HFV at 10, 20 and 45 min, but not at 30 min. PEEP was generated in all groups during HFV and was significantly lower with slower rates at each time interval. There was no significant change in the level of PEEP with time on HFV.

Haemodynamic data. There were no significant changes in heart rate, or in systolic, diastolic or mean arterial pressures on changing from CPPV to HFV or with time during HFV, and no significant differences between the groups at any time interval. Central venous pressure (CVP) increased on changing from CPPV to HFV at 150

TABLE II. *Mean (SEM) values of tidal volume (V_T) (ml) and mean driving pressures (DP) (bar) on CPPV and at 10, 20, 30 and 45 min following the start of HFV*

		CPPV	HFV			
		Time: 0	10	20	30	45
Group 1 80 b.p.m.						
	V_T	790	253.5	249.5	235.9	260.0
		(14.5)	(8.9)	(8.2)	(11.9)	(8.7)
	DP		3.7	3.4	3.56	3.56
Group 2 100 b.p.m.						
	V_T	685	176.4	181.5	182.8	183.1
		(21.2)	(10.7)	(10.6)	(11.3)	(13.2)
	DP		3.96	3.91	3.84	3.84
Group 3 150 b.p.m.						
	V_T	735	108.2	116.3	116.7	115.2
		(32.5)	(4.81)	(4.22)	(4.06)	(5.52)
	DP		4	4	4	4

TABLE III. *Mean (SEM) values of arterial oxygen tensions (Pa_{O_2}) and carbon dioxide tensions (Pa_{CO_2}) (kPa) on CPPV and at 10, 20, 30 and 45 min following the start of HFV. *$P < 0.001$ (when compared with the previous measurement)*

		CPPV	HFV			
		Time: 0	10	20	30	45
Group 1 80 b.p.m.						
	Pa_{O_2}	52.6	49.5	46.5	50.4	56.9
		(2.39)	(2.78)	(3.62)	(4.21)	(2.48)
	Pa_{CO_2}	4.11	4.12	4.60	4.75	4.58
		(0.25)	(0.24)	(0.26)	(0.26)	(0.37)
Group 2 100 b.p.m.						
	Pa_{O_2}	52.3	46.8	49.9	52.9	51.2
		(3.13)	(4.42)	(3.77)	(3.55)	(3.22)
	Pa_{CO_2}	4.10	4.39	4.73	4.62	4.66
		(0.14)	(0.23)	(0.28)	(0.21)	(0.18)
Group 3 150 b.p.m.						
	P_{aO_2}	52.5	52.5	53.5	54.8	57.2
		(3.36)	(4.71)	(4.01)	(4.29)	(3.19)
	Pa_{CO_2}	4.26	5.52*	5.87	5.72	6.16
		(0.16)	(0.16)	(0.20)	(0.19)	(0.15)

and 100 b.p.m. There was no subsequent change in CVP with time in any group, and no overall difference between the groups at any time interval (table V).

DISCUSSION

The laboratory investigations reported were carried out using a model lung which has been validated elsewhere and complies with ISO standards (Chakrabarti and Sykes, 1976). The pneumotachograph used in this study has been designed to reproduce 100% of each trace deflection up to a frequency of 4.2 Hz (252 cycle min^{-1}). Thus we limited our observations to ventilatory rates below 200 b.p.m.

The use of halothane to detect dilution of the anaesthetic gas with driving gas might be criticized, since it relies on the accuracy of the

TABLE IV. *Mean (SEM) values of peak airway pressure (peak* P_{aw}*), mean airway pressure (*$P_{\overline{aw}}$*) and positive end-expiratory pressure (PEEP) (mm Hg) on CPPV and at 10, 20, 30 and 45 min following the start of HFV.* *P < *0.01;* **P < *0.002 (when compared with the previous measurement)*

		CPPV	HFV			
	Time:	0	10	20	30	45
Group 1 80 b.p.m.						
	Peak P_{aw}	12.2	10.5*	11.0	11.9	9.3
		(1.36)	(1.19)	(1.15)	(1.34)	(1.38)
	$P_{\overline{aw}}$	6.1	4.8*	5.1	5.3	4.8
		(0.68)	(0.46)	(0.44)	(0.48)	(0.73)
	PEEP	0	2.0	2.1	2.1	2.5
			(0.67)	(0.23)	(0.27)	(0.5)
Group 2 100 b.p.m						
	Peak P_{aw}	11.5	9.55*	9.7	9.11	9.75
		(0.9)	(0.8)	(0.68)	(0.72)	(0.67)
	$P_{\overline{aw}}$	5.75	5.67	5.70	5.67	5.88
		(0.45)	(0.39)	(0.23)	(0.40)	(0.34)
	PEEP	0	3.7	3.7	3.94	3.94
			(0.37)	(0.3)	(0.32)	(0.27)
Group 3 150 b.p.m.						
	Peak P_{aw}	15.2	9.95**	9.54	9.37	9.89
		(1.46)	(0.97)	(0.58)	(0.56)	(0.60)
	$P_{\overline{aw}}$	7.60	6.33	6.43	6.37	6.55
		(0.73)	(0.37)	(0.36)	(0.35)	(0.36)
	PEEP	0	4.35	4.95	4.87	4.94
			(0.26)	(0.4)	(0.42)	(0.46)

TABLE V. *Mean (SEM) values of heart rate (HR) (beat* min^{-1}*), mean arterial pressure (MAP) (mm Hg) and central venous pressure (CVP) (mm Hg) on CPPV and at 10, 20, 30 and 45 min following the start of HFV.* *P < *0.02;* **P < *0.002 (when compared with the previous measurement)*

		CPPV	HFV			
	Time:	0	10	20	30	45
Group 1 80 b.p.m.						
	HR	65.7	66.7	72.1	75.9	75.5
		(2.51)	(2.89)	(3.21)	(4.25)	(8.06)
	MAP	83.6	87.9	88.9	85.6	81.0
		(3.22)	(5.22)	(4.17)	(4.10)	(2.97)
	CVP	2.4	4.0	4.2	4.3	5.5
		(1.01)	(0.93)	(1.06)	(0.96)	(2.18)
Group 2 100 b.p.m						
	HR	65.4	70.0	74.8	76.9	77.5
		(3.93)	(3.92)	(4.40)	(6.39)	(5.08)
	MAP	82.9	88.4	92.3	86.4	92.6
		(5.48)	(5.52)	(4.28)	(3.32)	(3.83)
	CVP	1.9	4.1*	4.8	4.0	5.3
		(0.55)	(0.71)	(1.11)	(1.12)	(0.82)
Group 3 150 b.p.m.						
	HR	70.3	65.1	68.2	70.9	73.1
		(3.89)	(4.24)	(3.56)	(4.38)	(6.08)
	MAP	73.5	86.6	87.7	81.4	81.0
		(4.84)	(5.14)	(3.49)	(3.16)	(4.06)
	CVP	3.70	6.6**	6.5	5.5	6.7
		(0.70)	(0.88)	(1.05)	(1.22)	(1.21)

vaporizer output, the speed and accuracy of the halothane analyser, and minimal uptake of halothane by the plastic of the breathing system. Our measurement and recording system could not detect any variability in halothane output from the vaporizer at the fresh gas flows and vaporizer setting used. The response time of the halothane analyser was not fast enough to detect breath-to-breath variability, particularly at the faster ventilatory rates tested. Nevertheless, by studying a minimum of 15 min at each setting, we were able to see a remarkably stable mean halothane concentration at the patient end of the breathing system. This enabled us to detect mixing of driving and anaesthetic gases, which occurred to an extent which might become clinically significant when the fresh gas flow to minute ventilation ratio was less than 1:3. In this context, since the ventilator driving gas was 100% oxygen, the consequence of mixing of anaesthetic and driving gases would be a reduction in anaesthetic gas and vapour concentrations and the risk of awareness during anaesthesia.

Tidal and minute volumes with HFV vary with the inspiratory flow rates and the inspiratory time (Sykes, 1985). In the study the tidal volumes were smaller at the faster rates because of the shorter inspiratory time for each ventilatory cycle. Since the inspiratory:expiratory ratio was the same in all patient groups during HFV the total inspiratory time per minute was constant (18 s). However, the minute ventilation and thus the inspiratory flow rate were lower at faster rates both in the clinical and the laboratory studies. This decrease in inspiratory flow with increasing frequency was secondary to rate-dependent changes in resistance (George and Geddes, 1985), PEEP (Carlon, Khan et al., 1981; Sykes, 1985) and the inertia of the lung and chest wall (Sykes, 1985).

In HFV with gas entrainment, the decrease in tidal volume is greater when airway resistance is increased than when lung compliance is reduced (Carlon, Khan et al., 1981; Carlon and Howland, 1985). This response to changing resistance and compliance was seen with this system, presumably because air was entrained by the jet at the distal end of the T-piece. It has been suggested that, during HFV, it is possible to maintain alveolar ventilation with a tidal volume less than anatomical deadspace (Klain and Smith, 1977; Butler et al., 1980; Rossing et al., 1981). Indeed, in this study, we have shown that adequate gas exchange can occur when delivered tidal volumes were approximately equivalent to those values of anatomical deadspace seen when measured during conventional mechanical ventilation. However, it has long been known that deadspace varies as a function of tidal volume (Severinghaus and Stupfel, 1957; Nunn and Hill, 1960) and, more recently, it has been established that, during HFV, deadspace volume decreases as tidal volume decreases until a minimum deadspace volume is reached (Chakrabarti, Gordon and Whitwam, 1986). We had difficulty maintaining Pa_{CO_2} within the normal range when tidal volumes decreased below approximately 2 ml kg^{-1}, and our experience to date suggests that this is the minimum satisfactory tidal volume with this system of ventilation.

In HFV there is inherent PEEP as a result of the inability of the lungs to recoil totally during the short expiratory phase (Sjostrand, 1980; Sykes, 1985) and PEEP increases with ventilatory rate (Klain and Smith, 1977; Sykes, 1985). The absolute values of PEEP recorded in this study were higher than those obtained with other systems of HFV (Jonzon et al., 1971; Normandale and colleagues, personal communication), and with a similar system (Whitwam et al., 1983). There is some evidence that PEEP is higher when the jet source is further from the carina and when the pressure waveform is damped (Calkins et al., 1983), both of which apply to the system described here. However, the measurements reported with other systems have been made under clinical conditions different from those in this study.

In this study, minimum $P_{\overline{aw}}$ during HFV was achieved at 80 b.p.m. This is in agreement with other reports in which $P_{\overline{aw}}$ has been shown to increase with increasing ventilatory rates above 60 b.p.m. (Gioia and Rogers, 1985) and with increasing PEEP (Carlon, Ray et al., 1981). Furthermore, the decreases in peak P_{aw} seen in this study are in agreement with those observed using similar (Whitwam et al., 1983) and other (Normandale and colleagues, unpublished observations) methods of delivering HFV.

The haemodynamic stability observed during HFV is in agreement with previous reports (Jonzon et al., 1971; Klain and Smith, 1977; Gillespie, 1983).

In conclusion, we are able to confirm previous work that suggests that that using a jet source as a pneumatic piston on the expiratory limb of a

T-piece system is a suitable method for delivering anaesthetic gases and vapours to patients at high ventilatory rates (Whitwam et al., 1983). At 80 and 100 b.p.m. it can provide adequate ventilation of the lungs with lower peak and mean airway pressures than can be achieved on CPPV and without haemodynamic impairment. This system is simple in concept and has the advantage of being easily constructed from components that are currently commercially available. When compared with other HFV systems, it requires a modest fresh gas input (Sjostrand, 1980) and at 100 ml kg^{-1} there is no contamination of the gas entering the lung by the driving gas. It is relatively quiet with the muffler in place and can be adapted for manual ventilation by placing an open-tailed reservoir bag on the distal limb. The component parts are either disposable or can be sterilized. Waste gases can be scavenged easily.

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PULMONARY OEDEMA FOLLOWING AIRWAY OBSTRUCTION IN A PATIENT WITH HODGKIN'S DISEASE

S. L. PRICE AND B. R. HECKER

SUMMARY

We report a case of pulmonary oedema following airway obstruction in a patient who underwent biopsy of a tumour involving the anterior mediastinum and neck. The occurrence of airway obstruction in patients with anterior mediastinal masses, and the pathogenesis of pulmonary oedema occurring in association with airway obstruction, are discussed.

Airway obstruction is a known complication of the presence of an anterior mediastinal mass, and may complicate the perioperative course of patients undergoing biopsy or resection. Pulmonary oedema has been reported to occur in patients with airway obstruction resulting from acute epiglottitis and croup (Travis, Todres and Shannon, 1977; Soliman and Richer, 1978; Galvis, Stool and Bluestone, 1980), laryngospasm (Cozanitis et al., 1982; Lee and Downes, 1983; Weissman, Damask and Yang, 1984), strangulation (Oswalt, Gates and Holstrom, 1977), or tumour (Oswalt, Gates and Holstrom, 1977; Leatherman and Schwartz, 1983). Such oedema may be caused, at least in part, by changes in the Starling forces, as a result of the negative intrathoracic pressure, favouring the net movement of fluid out of the pulmonary vasculature and into the interstitium and alveoli. We report a case of pulmonary oedema following airway obstruction in a patient who had undergone biopsies of mediastinal nodes and tumour.

CASE REPORT

A 27-yr-old female with mediastinal adenopathy presented for mediastinoscopy. She was asymptomatic and had no other known medical problems. Physical examination was unremarkable. Computerized tomography demonstrated a mass in the upper anterior mediastinum extending from the pulmonary artery to the thyroid gland. A left supraclavicular node biopsy performed under general anaesthesia 1 month earlier at another hospital had been uneventful, but inconclusive.

After preoxygenation, anaesthesia was induced with thiamylal and ventilation controlled. Suxamethonium was administered and tracheal intubation accomplished without difficulty. Anaesthesia was maintained with nitrous oxide and isoflurane in oxygen. No other neuromuscular blocking agent was administered. The initial incision revealed the presence of tumour infiltrating the strap muscles of the neck and the thyroid gland. Plans for mediastinoscopy were cancelled. In addition to tissue biopsy, dissection around the thyroid gland and trachea was carried out to determine the extent of tumour involvement.

At the end of the procedure, the patient was breathing spontaneously and awake enough to open her eyes on command before removal of the tracheal tube. Immediately after extubation, ventilation was noted to be inadequate despite vigorous inspiratory effort. Jaw lift, insertion of an oropharyngeal airway and an attempt at positive pressure ventilation all failed to improve ventilation. The patient became cyanotic and her heart rate decreased to 50 beat min^{-1}. The trachea was re-intubated and mechanical hyperventilation with 100% oxygen instituted. The vocal cords and proximal trachea appeared normal at the time of re-intubation.

Within 5 min of reintubation, bilateral rhonchi were noted and copious pink frothy secretions were suctioned from the tracheal tube. Secretions were not tenacious and no mucus plugs were

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identified. The patient was transferred to the recovery room where she was sedated, paralysed and mechanically ventilated with 100% oxygen and 5 cm H_2O of positive end-expiratory pressure (PEEP). A chest x-ray demonstrated a patchy right-sided infiltrate. Arterial blood-gas tensions (100% oxygen and 5 cm H_2O PEEP) were: pH = 7.37, $Pa_{O_2} = 73.9$ kPa, $Pa_{CO_2} = 5.5$ kPa. Dexamethasone 10 mg was administered, as was frusemide 10 mg, although the patient had received only 800 ml of i.v. crystalloid during the 1-h procedure.

She was transferred to the intensive care unit where mechanical ventilation was continued overnight. Chest x-ray the following morning showed that the pulmonary infiltrate had cleared. The trachea was extubated, and the patient was seen to maintain adequate spontaneous ventilation. The remainder of the postoperative course was uneventful. She was discharged home on the 3rd day after operation to undergo outpatient radiation therapy for mediastinal Hodgkin's disease.

DISCUSSION

This case illustrates two uncommon, but potentially lethal, complications: acute airway obstruction and non-cardiogenic pulmonary oedema. Numerous case reports in the literature document the hazards of general anaesthesia in patients with mediastinal involvement by Hodgkin's disease or other lymphomatous tumours which may compress or distort the extra- or intrathoracic trachea or mainstem bronchi (Meeker et al., 1972; Bittar, 1975; Piro, Weiss and Hellman, 1976; Keon, 1981; Neuman et al., 1984). Paralysis and loss of spontaneous ventilation may cause previously compensated patients to develop severe symptomatic obstruction (Gordon, 1972; Bittar, 1975) possibly as a result of the loss of the negative intrathoracic pressure which tends to dilate intrathoracic airways during inspiration, and of loss of bronchial smooth muscle tone thus increasing compressibility of large airways during expiration (DeGraff and Bouhuys, 1973). In the postoperative period, obstruction may also be caused by oedema or by erosion or weakening of the cartilaginous rings of the trachea by tumour. The trachea may then collapse when the supporting tissue is removed, such as following removal of a substernal goitre (Gordon, 1972; Shambaugh, Seed and Korn, 1973).

Our patient had no signs or symptoms of airway compromise before surgery and no airway problems were encountered on induction or initial intubation. We believe that surgical dissection alone may have compromised the tissue supporting the trachea and may also have caused oedema to form, resulting in critical airway obstruction.

Pulmonary oedema has been reported to occur in association with upper airway obstruction, particularly in children (Oswalt, Gates and Holstrom, 1977; Travis, Todres and Shannon, 1977; Soliman and Richer, 1978; Galvis, Stool and Bluestone, 1980; Cozanitis et al., 1982; Leatherman and Schwartz, 1983; Lee and Downes, 1983; Weissman, Damask and Yang, 1984). It is not clear why oedema was demonstrated radiographically only in the right lung. Aspiration may be considered. However, the patient had taken nothing by mouth for at least 12 h and was not noted to have aspirated. No evidence of gastric contents was seen on re-intubation, nor on suctioning of the trachea. Furthermore, the initial severity of the oedema, with recovery in less than 24 h, was more consistent with pulmonary oedema than with aspiration.

The mechanism of pulmonary oedema following airway obstruction is not clear, and may be related to a combination of factors including changes in hydrostatic pressures across the pulmonary vascular membrane, change in pulmonary capillary permeability, and lymphatic obstruction by tumour.

Starling's equation for fluid transport relates the flow of fluid across a membrane, in this case the alveolocapillary membrane, to the gradients between the hydrostatic and osmotic pressures in the pulmonary microvasculature and perimicrovascular (interstitial) space (Staub, 1974). It is not likely that osmotic pressures were acutely altered in this case. The patient was well nourished and had a normal serum protein concentration. Blood loss and evaporative fluid loss during the procedure were minimal. The only fluid administered was a modest amount of crystalloid solution.

On the other hand, a change in the hydrostatic gradient was probably a major factor in the formation of the oedema. Several mechanisms may have been responsible for this change.

Transmission to the interstitial space of negative intrapleural pressure, generated by inspiratory efforts against an obstructed airway, would increase the hydrostatic pressure gradient, promoting movement of fluid out of the pulmonary vasculature and into the interstitial space. Stalcup and Mellins (1977) believe this mechanism may enhance oedema formation during asthmatic attacks. These authors measured mean pleural pressures of up to -25.5 cm H_2O and peak inspiratory pressures of -38.8 cm H_2O in asthmatic children. A similar mechanism may be responsible for unilateral pulmonary oedema resulting from the rapid re-expansion of a pneumothorax by application of highly negative pressure to the pleural space (Childress, Moy and Mottram, 1971).

The hydrostatic gradient may also have been increased secondary to an increase in pulmonary microvascular pressure. Hypoxia sufficient to produce cyanosis and bradycardia in our patient may have triggered a massive sympathetic discharge, resulting in a shift of blood from the systemic to the pulmonary circulation. This would increase pulmonary vascular pressures and might also injure pulmonary vessels, causing increased pulmonary capillary permeability. Theodore and Robin (1975, 1976) have suggested this mechanism to explain neurogenic pulmonary oedema and high altitude pulmonary oedema. Hypoxia may also have caused vasoconstriction of a significant portion of the pulmonary vascular bed, forcing blood through the remaining vessels at pressures sufficiently high to result in oedema. This mechanism has been proposed by Staub (1974) to explain high altitude pulmonary oedema.

Nitrous oxide is also known to cause pulmonary vasoconstriction, but is unlikely to have been a significant factor in our patient for two reasons. First, although nitrous oxide was used, the patient was ventilated with 100% oxygen for several minutes before extubation of the trachea; thus, little or no nitrous oxide was present at the time of the airway obstruction. Second, it appears that nitrous oxide causes a significant increase of pulmonary vascular resistance only in patients with pre-existing pulmonary hypertension (Shulte-Sasse, Hess and Tarnow, 1982)—which our patient did not have.

Altered ventricular function may also be important in the pathogensis of this syndrome as Leatherman and Schwartz (1983) suggested. The Muller manoeuvre (inspiration against a closed glottis), which is similar to the inspiratory efforts against an obstructed airway which we observed in our patient, has been shown to cause left ventricular dysfunction (Buda et al., 1979). This effect, added to myocardial depression resulting from acidosis, may have caused sufficient left ventricular dysfunction to increase pulmonary capillary pressures and promote oedema formation in our patient.

Another factor to consider is the pulmonary microvascular membrane itself which may have been altered, resulting in increased pulmonary capillary permeability such as is seen in the adult respiratory distress syndrome (ARDS). It is conceivable that our patient suffered some capillary damage, contributing to the flux of fluid across the alveolocapillary membrane in the presence of a large hydrostatic gradient. However, we doubt that increased permeability played a major role in the formation of the oedema, since one would not expect the oedema to resolve as rapidly as it did in the presence of severe capillary endothelial damage. Any capillary damage must have been of sufficiently minor nature that, when hydrostatic forces returned to normal, the pulmonary lymphatics were able to compensate and prevent further collection of oedema fluid in the alveoli.

It is possible that our patient's tumour may have partially obstructed pulmonary lymphatic outflow, delaying the normal removal of fluid and contributing to pulmonary oedema at a time of transiently increased passage of fluid across the alveolocapillary membrane. Lymphatic obstruction, if present, clearly was not complete since no oedema was detected before surgery, and was cleared within 24 h of the acute insult.

In summary, we have reported a case of pulmonary oedema following airway obstruction in a patient with an anterior mediastinal mass. This illustrates the importance of being alert to the possibility of airway obstruction as a result of oedma or removal of anterior supporting tissue in patients with mass lesions and in patients undergoing operative manipulation of the upper airway. Furthermore, it illustrates that upper airway obstruction may be a cause of pulmonary oedema, which is often treatable with oxygen and positive end expiratory pressure.

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CORRESPONDENCE

ISOFLURANE IN DENTAL ANAESTHESIA FOR CHILDREN

Sir,—Two papers in the April 1986 issue of the Journal confirm the findings of earlier studies that isoflurane may cause more airway irritation than halothane. Although the results of the two reports are by no means dissimilar, the authors arrive at quite different conclusions as to the usefulness of the newer agent. McAteer and his colleagues believe that isoflurane provides a satisfactory alternative to halothane for use in the paediatric outpatient dental clinic, although offering no clear-cut advantage. Cattermole and his associates, on the other hand, take the view that it cannot be recommended because of the effects of its pungency.

The airway irritation caused by isoflurane may be minimized by the i.v. induction of anaesthesia. However, volatile agents are clearly convenient for use in infants and small children in whom venous access may not always be readily available before the induction of anaesthesia. It is in these circumstances, when isoflurane is used as the main agent in the unpremedicated child, that increased secretions and coughing may be troublesome. This is unfortunate because isoflurane would seem to have important advantages to offer: by its use the drawbacks of halothane such as the onset of ventricular arrhythmias, adrenaline incompatability and the hazard, albeit remote, of hepatotoxicity, are largely circumvented. Other desirable features of isoflurane, although not readily apparent during clinical use, such as its low oil/gas partition coefficient with reduced implications of toxicity, metabolic stability and minimal impairment of myocardial contractility, should be kept in mind.

Isoflurane may well be the last inhalation agent to be marketed during the next few years. It would seem that its use in paediatric practice has yet to be fully determined and may well depend upon the extent to which anaesthetists are willing to tolerate a rather less smooth induction than with halothane in order to gain the benefits it has to offer.

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CARDIAC ARREST FOLLOWING I.V. VERAPAMIL COMBINED WITH HALOTHANE ANAESTHESIA

Sir,—Halothane and verapamil depress cardiac contractility and interfere with electrical conduction (Reves et al., 1982). The potential problems of anaesthesia in patients receiving calcium-channel blockers have been emphasized (Prys-Roberts, 1984) and in a recent report in the Journal Ramsay and colleagues (1986) demonstrated a decrease in cardiac performance in dogs after verapamil administered i.v. during halothane anaesthesia.

We report a case of cardiac arrest in association with halothane anaesthesia preceeded by verapamil i.v. A 56-year-old male treated with digoxin because of atrial fibrillation, was admitted to the hospital with haematemesis and melaena caused by gastric haemorrhage. Clinically he was shocked: arterial pressure 80/50 mm Hg; heart rate 150 beat min^{-1} in atrial fibrillation. Serum potassium concentration was within normal limits. Since it was impossible to correct the bleeding with blood transfusion, a laparotomy was performed. Anaesthesia was induced with ketamine 50 mg i.v. followed by suxamethonium 150 mg to facilitate tracheal intubation. Anaesthesia was maintained with nitrous oxide in oxygen 2:1 via a circle system, supplemented with fentanyl 0.2 mg i.v. After haemostasis, the arterial pressure increased to 140/80 mm Hg. Because of persisting atrial fibrillation (heart rate of 160 beat min^{-1}), verapamil 5 mg was administered i.v., and resulted in a decrease in heart rate to 110 beat min^{-1}. Ten minutes later 0.5% halothane was added to the gas mixture; profound hypotension was evident after 5 min with signs of ischaemia (S–T depression) and first degree heart block (prolonged P–R interval), and was followed by cardiac arrest. Open chest cardiac compression was commenced in combination with the administration of noradrenaline, atropine and calcium i.v. Cardiac output returned within 1 min and the patient was hyperventilated for 24 h, after which the recovery was uneventful. The patient was discharged from the hospital 10 days later without neurological sequelae. ECG and creatine kinase isoenzyme revealed no evidence of myocardial infarction.

The most likely reason for the event was the additive depressant effects of halothane and verapamil on global cardiac function as assessed in laboratory studies (Kapur and Flacke, 1981; Kapur et al., 1984), justifying caution in the simultaneous use of these two drugs.

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TREATMENT OF THYROID STORM IN A CHILD WITH DANTROLENE

Sir,—We would like to report a case of thyroid storm in a child in whom tachycardia and increasing temperature—despite maximal conventional treatment—was treated with dantrolene.

The patient, a 3½-year-old girl (weight 12 kg) was admitted to the pediatric department, where thyroid storm was diagnosed. The patient had goitre, exophthalmos and extremely increased thyroid function test values. X-ray examination of the chest revealed cardiac enlargement. The patient was treated with propylthiouracil and propranolol orally and sodium iodide i.v. for 5 days, and these normalized thyroid function. In spite of this treatment, recurrent episodes with hyperpyrexia and tachycardia remained. The patient developed cardiac and ventilatory failure, and was transferred to the intensive care unit. Maintenance of adequate arterial oxygen tension was difficult even with artificial ventilation with positive end-expiratory pressure. Treatment with digoxin, frusemide, steroids and antibiotics was initiated. Tachycardia and hyperthermia persisted and the dose of propranolol was increased to 1 mg × 6 per day i.v. Sedation, neuromuscular blockade and active cooling were commenced to control fulminant hyperthermia. The dose of i.v. propylthiouracil was increased and i.v. sodium iodide recommenced, because of increasing evidence of thyroid dysfunction. In spite of these measures and treatment with nitroglycerin i.v., the temperature increased again, tachycardia continued and the condition of the patient deteriorated. Dantrolene sodium 10 mg was given i.v. once an hour for 3 h. This dosage was repeated 3 h later. Twelve hours after start of this treatment, the temperature had decreased from 39 °C to 34 °C, and the heart rate was reduced from 140 beat min^{-1} to 90 beat min^{-1}. Concomitant with the decrease in temperature we measured a 30% decrease in $\dot{V}\text{CO}_2$ measured with a carbon dioxide analyser (930: Siemens–Elema, Sweden). Dantrolene was continued for 2½ days and a total of 180 mg was given. The temperature and heart rate were controlled thereafter with conventional therapy. The patient died 12 days later in irreversible ventilatory and renal failure.

Thyroid hormones increase protein and ribonucleic acid synthesis (Symons, 1979). The earliest action of thyroid hormones is to accelerate the basal respiratory rate (BRR) of the mitchondria. Dantrolene sodium, a drug efficacious in the treatment of acute malignant hyperthermia, prevents release of calcium from the sarcoplasmic reticulum (Britt, Scott and Frodis, 1984). The exact site of action of the drug is not known, even though it could be a direct effect on the sarcoplasmic reticulum, or indirect on the T-system or exitation–contraction coupling. Alternatively, dantrolene might alter some calcium-related function of mitochondria and, thereby, control BRR.

Fulminant heat stroke has been treated with dantrolene with excellent results (Lydiatt and Hill, 1981). The heat stroke syndrome and malignant hyperthermia have apparent relationships (Jardon, 1982), and the clinical symptoms of these syndromes have apparent similarities with those of thyroid storm (Stevens, 1983).

The present case report indicates that treatment with dantrolene sodium should not be reserved for cases of malignant hyperthermia, but might be considered in cases of thyroid storm, especially when other therapy fails.

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LONG TERM USE OF THE VOCALAID TRACHEOSTOMY TUBE FOR TRACHEAL TOILET

Sir,—We wish to report the use of the Vocalaid tracheostomy tube (Portex Ltd, Hythe, Kent) to prevent pulmonary aspiration over a period of 18 months. A 42-year-old man with progressive motor neurone disease and resultant bulbar palsy with deteriorating pharyngeal and laryngeal reflexes presented to this Intensive Care unit with pneumonia following aspiration. Controlled mechanical ventilation was required. His subsequent management included the formation of a permanent tracheostomy. He recovered from his pneumonia, but the problem of continued aspiration of food (as semi-solids) and saliva remained. This would not be prevented by a tracheostomy tube with a high-volume low-pressure cuff, even if the patient were being fed via a fine-bore nasogastric tube (Macrae and Wallace, 1981; Boscoe and Rosin, 1984). Surgical prevention by epiglottoplexy (Montgomery, 1975) was considered; however, a more conservative approach was adopted using a Vocalaid tracheostomy tube. This tracheostomy tube has an additional pilot tube with an aperture immediately above the cuff (fig. 1). Compressed gas can be blown down this additional tube to allow patients to phonate. We utilized this port to apply continuous suction, preventing the collection of

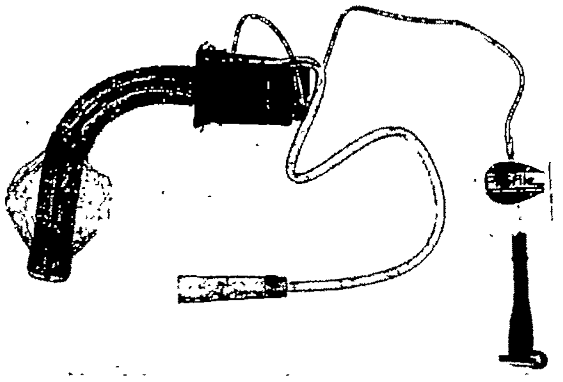

FIG. 1. The Vocalaid tracheostomy tube incorporating two pilot tubes.

saliva and food above the cuff and its subsequent aspiration. Short term use of a modified speaking tracheostomy tube for the same purpose has been reported previously (Shahvari, Kigin and Zimmerman, 1977).

As recovery from the pneumonia occurred continuous aspiration proved unneccessary and, latterly, it has only been applied during feeding.

The manufacturers subsequently supplied us with a specially modified Vocalaid with two tubes ending as apertures above the cuff, so that suction could be applied to one and the insufflation of compressed gas to the other, to enable speech. Unfortunately, this was only partially successful as a result of the underlying disease, and its use was abandoned.

We were initially sceptical of these measures in a patient with a severely disabling progressive illness, but the use of this device in the manner described has successfully prevented pulmonary aspiration for 18 months. During this period the patient has travelled widely and returned to his original occupation. This technique may be applicable to other such patients and may avoid the need for surgical intervention.

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ESTIMATION OF NASOTRACHEAL TUBE LENGTH IN INFANTS AND CHILDREN

Sir,—Nasotracheal intubation is a well accepted routine practice when prolonged ventilatory support is necessary in children (Loomis, 1983). In order to formulate some basis for predetermining the correct length of the tracheal tube before intubation, all data on intubation collected from patients admitted to the Intensive Care Unit were analysed. This study covered a 1-yr period from August 1984 to July 1985 and included 634 patients.

The intubation technique at The Hospital for Sick Children has been described previously (Battersby, Hatch and Towey, 1977; Hatch and Sumner, 1981). Data relating to intubation are noted routinely on a ventilatory data sheet which is kept for each patient whilst they remain intubated. Data sheets of all patients requiring ventilatory support during the study period were reviewed. Data were specifically excluded if they referred to intubation for airway pathology. Some patients were reintubated because the initial tube dimensions were not clinically acceptable and in these only the optimal size nasotracheal tube dimensions for that patient were included in the study.

Analysis showed that the population under study (table I) was considerably under weight with respect to age and equated approximately to the 10th centile on normal growth charts (Tanner, Whitehouse and Takaishi, 1966; Gairdner and Pearson, 1971).

Analysis of tracheal tube sizes is presented in the form of the

TABLE I. *Patient details and analysis of nasotracheal tube size*

Age group (yr)	No.	Mean weight (kg)	Mode (range) of tube size	Anticipated tube size (i.d. mm) = $\frac{16 + \text{Age (yr)}}{4}$
0–1/52	118	2.9	3.0 (2.5–3.5)	2.5–3.0
1/52–6/12	133	4.1	3.0 (2.5–4.0)	3.0–3.5
6/12–1	55	7.1	4.0 (3.5–4.5)	3.5–4.0
2	48	9.6	4.5 (3.0–5.0)	4.5
3	26	12.2	5.0 (3.0–5.0)	4.5–5.0
4	29	14.7	5.0 (4.5–6.0)	5.0
5	26	16.5	5.0 (4.5–6.0)	5.0–5.5
6	13	18.4	5.5 (4.5–6.0)	5.5
7	10	21.5	6.0 (5.0–6.0)	5.5–6.0
8	10	22.6	6.0 (5.5–6.5)	6.0
9	6	26.0	6.5 (6.0–7.0)	6.0–6.5
10	8	26.7	6.0 (6.0–7.0)	6.5
11	2	30.0	— (6.0–6.5)	6.5–7.0
12	8	31.9	7.0 (6.0–7.0)	7.0
13	5	34.0	7.0 (6.0–7.0)	7.0–7.5
14	3	34.3	— (6.5–7.5)	
15	3	38.0	7.0 (6.5–7.0)	
16	0	—	— —	
17	2	45.0	7.0 7.0	
18	1	54.0	— 7.0	

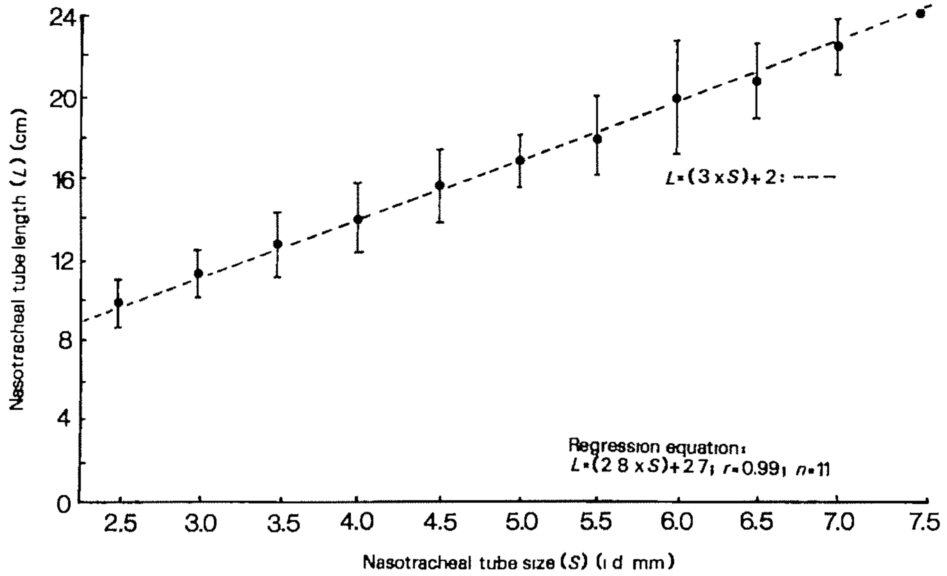

FIG. 1. Mean length (with 95% confidence limits) of each size of nasotracheal tube used. The regression equation is given for the relationship between length L and size S and the broken line representing $L = (3 \times S) + 2$ is shown (---) superimposed on the mean values.

TABLE II. *Recommended nasotracheal tube dimensions*

		Tube length (L) (cm)		
Age (yr)	Tube size (S) (i.d. mm)	This study (3S + 2)	Rees (1966)	Steward (1979)
0–3/12	2.5–3.0	9.5–11.0	11.8	13.5
4–7/12	3.0–3.5	11.0–12.5	12.6	14.0
8–11/12	3.5–4.0	12.5–14.0	13.6	
1	4.0	14.0	14.5	15.0
2	4.5	15.5	15.2	16.0
3	4.5–5.0	15.5–17.0	15.6	
4	5.0	17.0	16.5	17.0
5	5.0–5.5	17.0–18.5	16.8	
6	5.5	18.5	17.1	19.0
7	5.5–6.0	18.5–20.0	17.8	
8	6.0	20.0	18.3	21.0
9	6.0–6.5	20.0–21.5	18.8	
10	6.5	21.5	19.1	22.0
11	6.5–7.0	21.5–23.0	19.1	
12	7.0	23.0		22.0

mode and range (table I). Good agreement was obtained when compared with the anticipated tube size as calculated for each group on the basis of the formula used by Morgan and Steward (1982):

$$\text{Internal diameter (mm)} = \frac{16+\text{age(yr)}}{4}$$

Figure 1 illustrates the relationship of nasotracheal tube size, S (where S = internal diameter in mm) to length L (cm). The regression equation is unwieldy for everyday use, but the broken line (---) as shown in figure 1 can be obtained if, instead, one substitutes the equation:

$$L = (3 \times S) + 2$$

Various authors (Coldiron, 1968; Matilla et al., 1971, Tochen, 1979) have proposed correlates to predetermine the optimal depth to which the tracheal tube should be inserted, but these have proved cumbersome in use. We propose a simple formula as a guideline for calculating the length of the nasotracheal tube from its size:

$$L = (3 \times S) + 2$$

where L = length (cm) and S = internal diameter (mm). Clearly, the reliability of this formula depends on the selection of a tube of the correct diameter. We found that the tube sizes (diameters) selected were clinically satisfactory, and were predictable from the formula:

$$S = \frac{16 + \text{age(yr)}}{4}$$

It is important to note that the underweight nature of the population did not influence the length of tube as selected by this formula.

Analysis of reintubations for incorrect length supported the application of this guideline as in only two patients would the length have proved inappropriate as calculated by the formula.

$$L = (3 \times S) + 2$$

We propose a range of suitable nasotracheal tube lengths as applicable to infants and children heavier than 3 kg (table II). This is shown in comparison with previous recommended tables of length, some of which appear to be inappropriately long in children younger than 1 yr. The apparent discrepancy may be related to different methods of tube fixation, which leave a short length of tube extending from the nostril (Loomis, 1983). This proposed range of lengths is presented as a guide only because, as has always been the case, the length of every tracheal tube should be verified clinically and radiologically.

A. P. YATES
A. J. HARRIES
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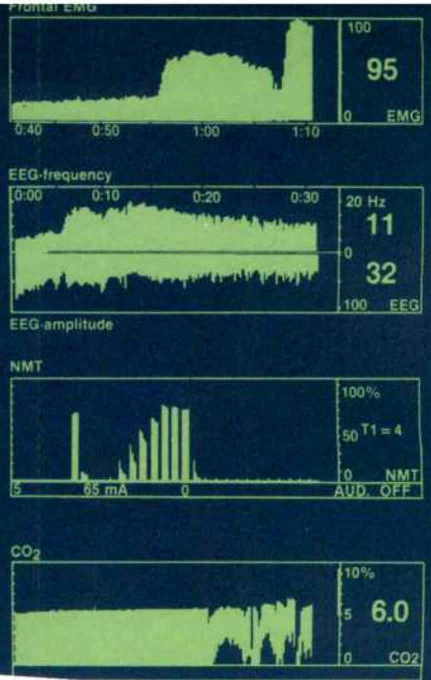

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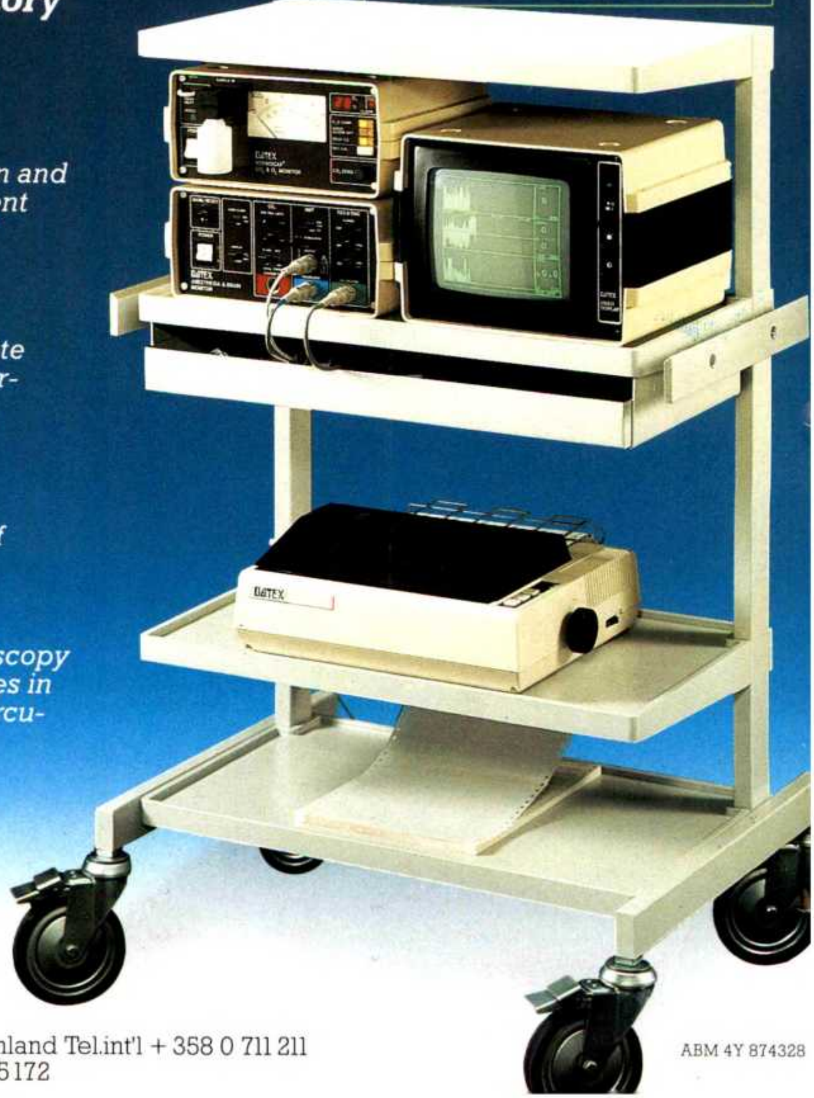

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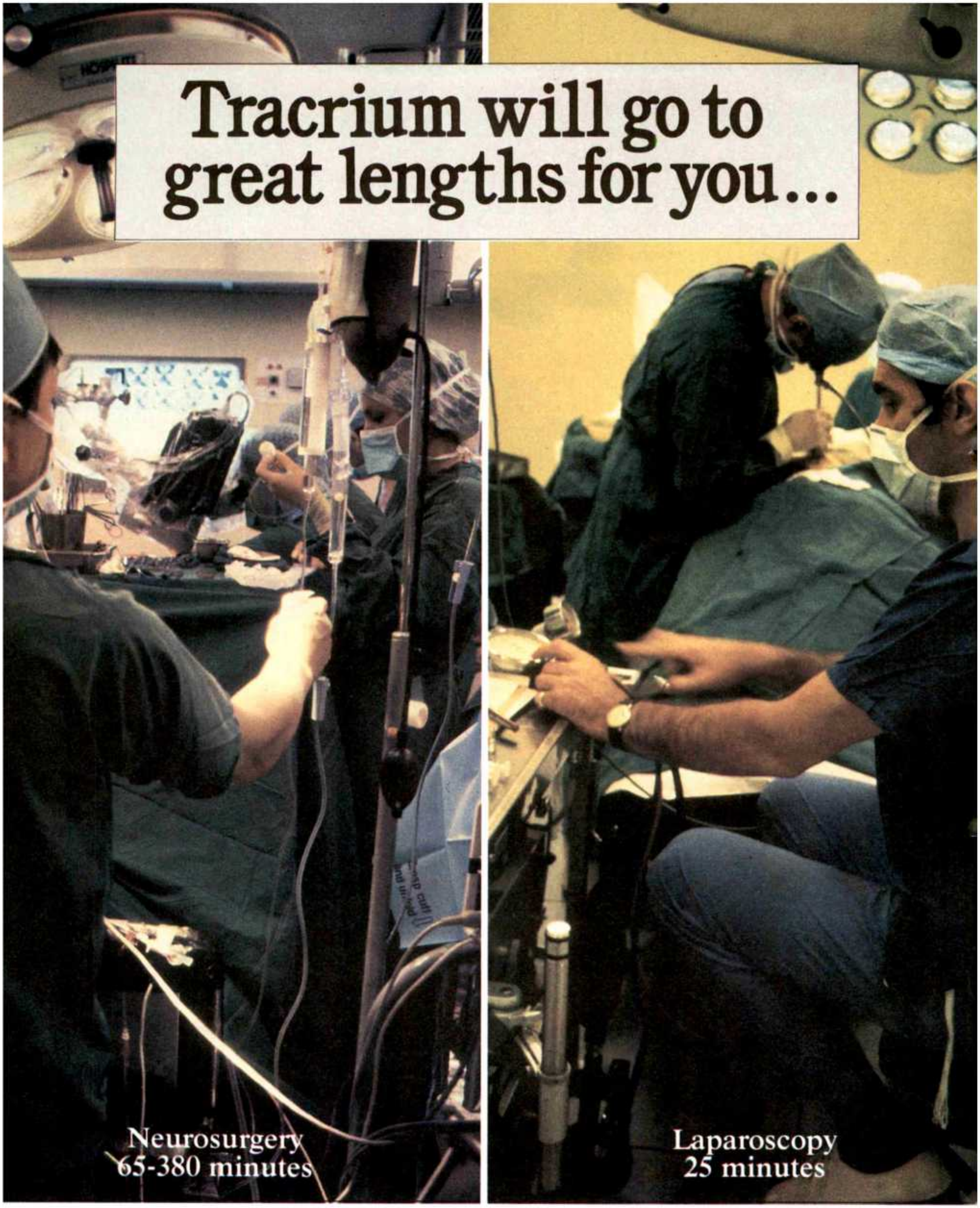

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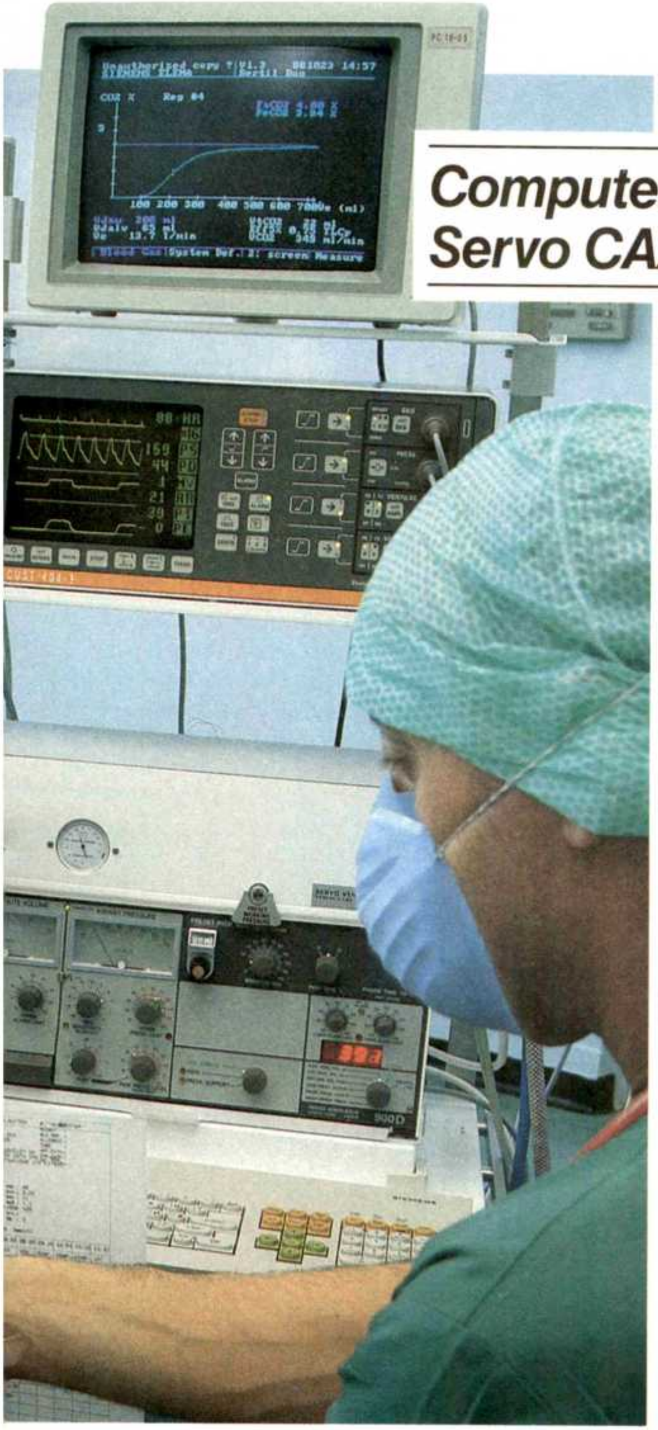

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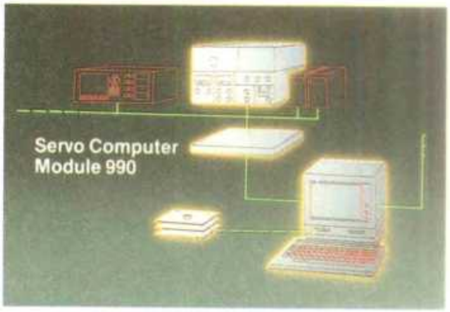

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Title page
Summary
Introduction (not headed)
Methods
Results
Discussion
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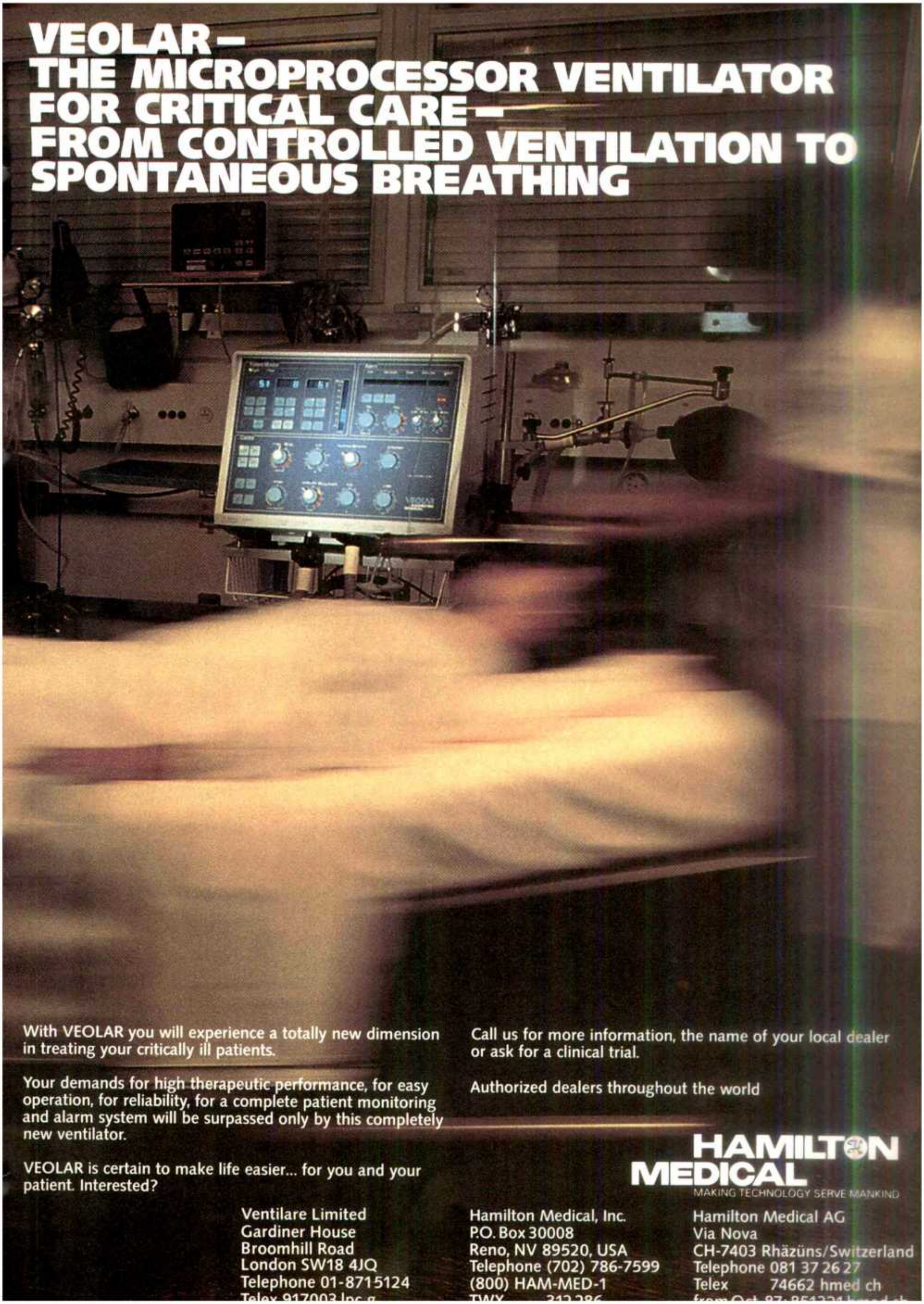
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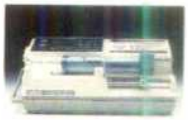

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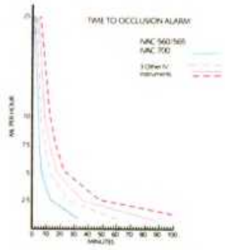

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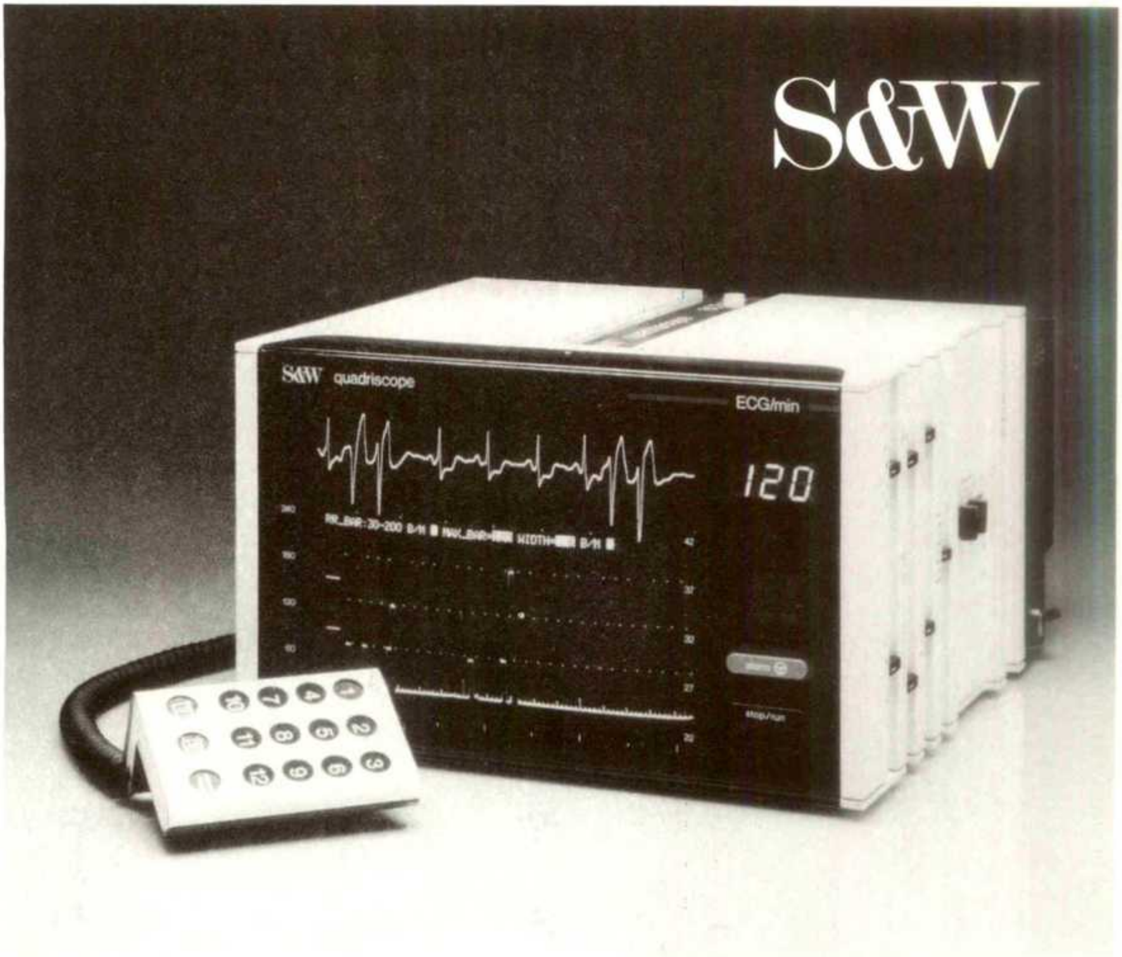

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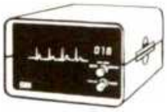

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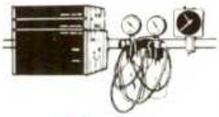

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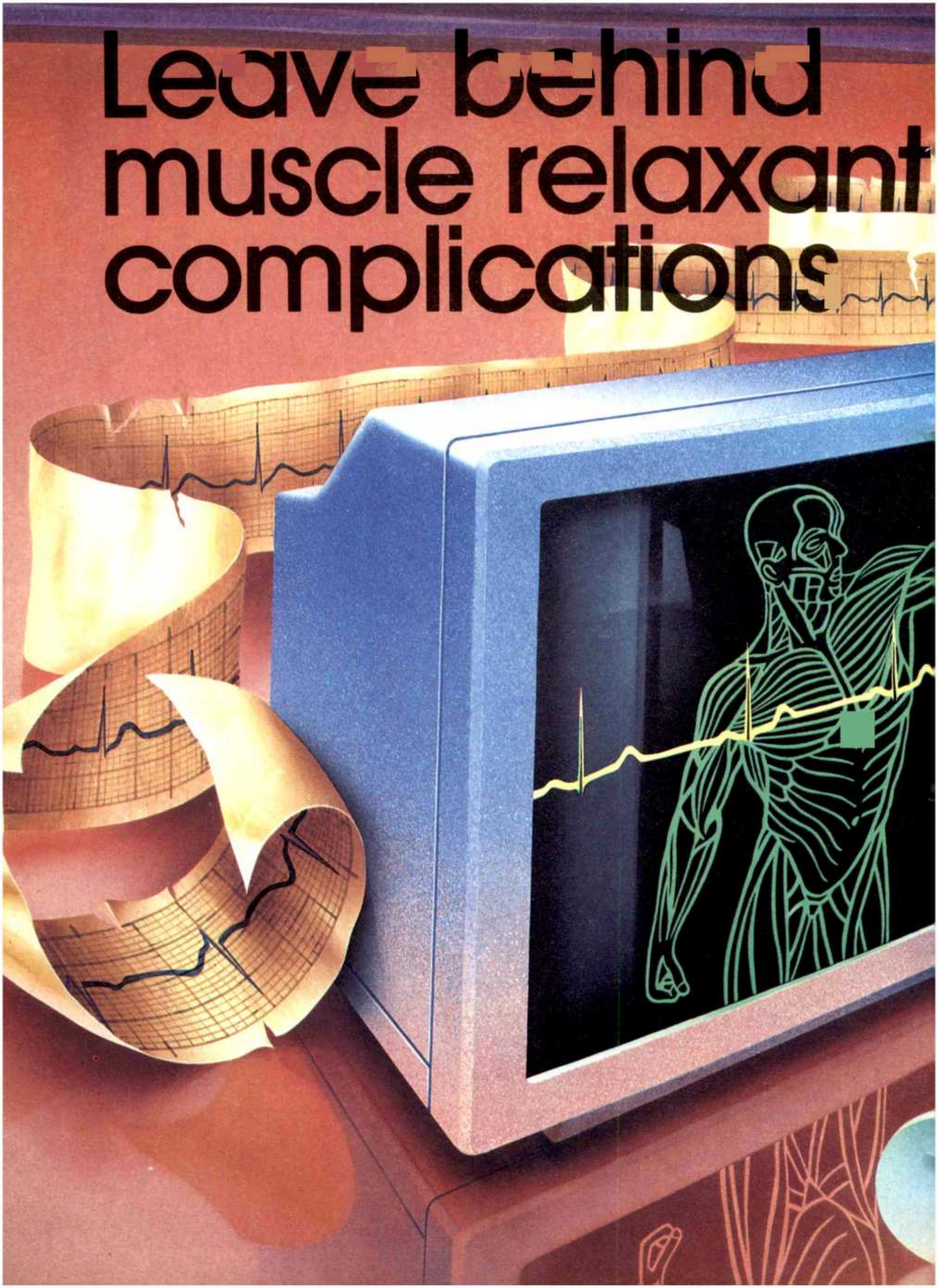

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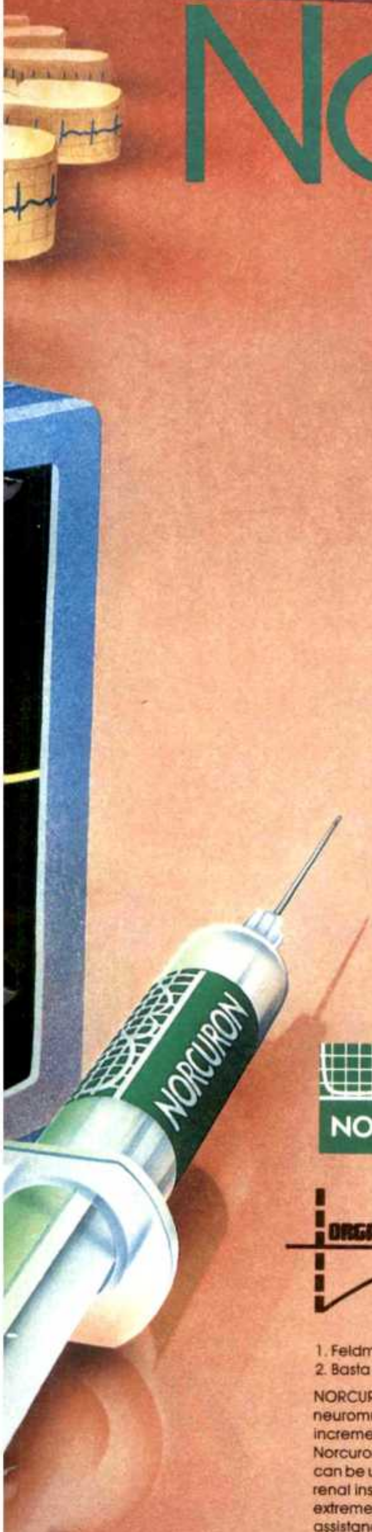

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1. Feldman SA; Clinical Experiences with Norcuron, Excerpta Medica (1983) 199-200
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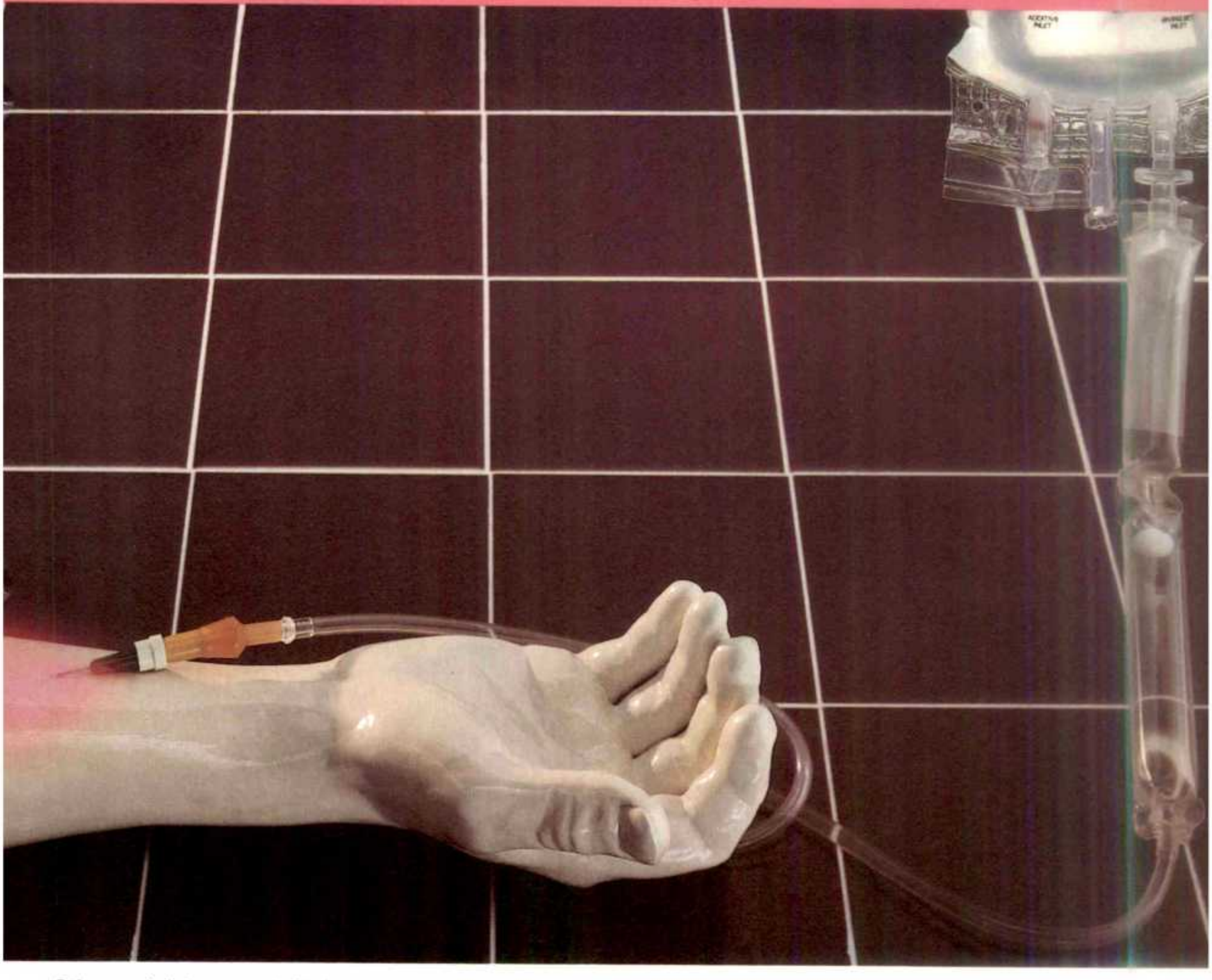

References **1.** S. Lazrove, *et al., Crit. Care Med.,* 1980, *8(5).* **2.** V.K. Puri, *et al.* Data on file. **3.** V. Hempel, *et al., Anaesthetist,* 1975, *24,* 198-201. **4.** M. T. Haupt and E.C. Rackow, *Crit. Care Med.,* 1982, *10,* 159-162. For full prescribing information see next page. Distributed for American Hospital Supply by Du Pont (UK) Ltd. For further information contact Du Pont (UK) Ltd., Pharmaceuticals, Wedgwood Way, Stevenage, Herts, SG1 4QN, Tel. (0438) 734549.

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ERRATA

Br. J. Anaesth. (1986), **58**, 1440

Materials and Methods, paragraph 3: The fourth sentence should read:

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(*not* Two 100-µl ...)

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Figure 2, p. 4: The last line on the figure should read

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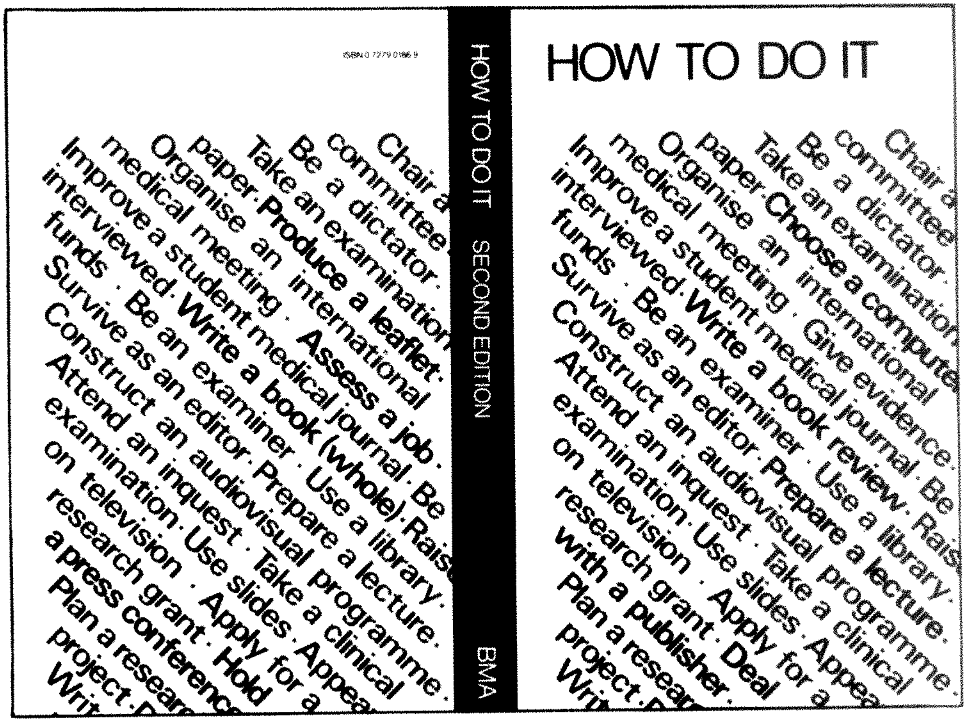

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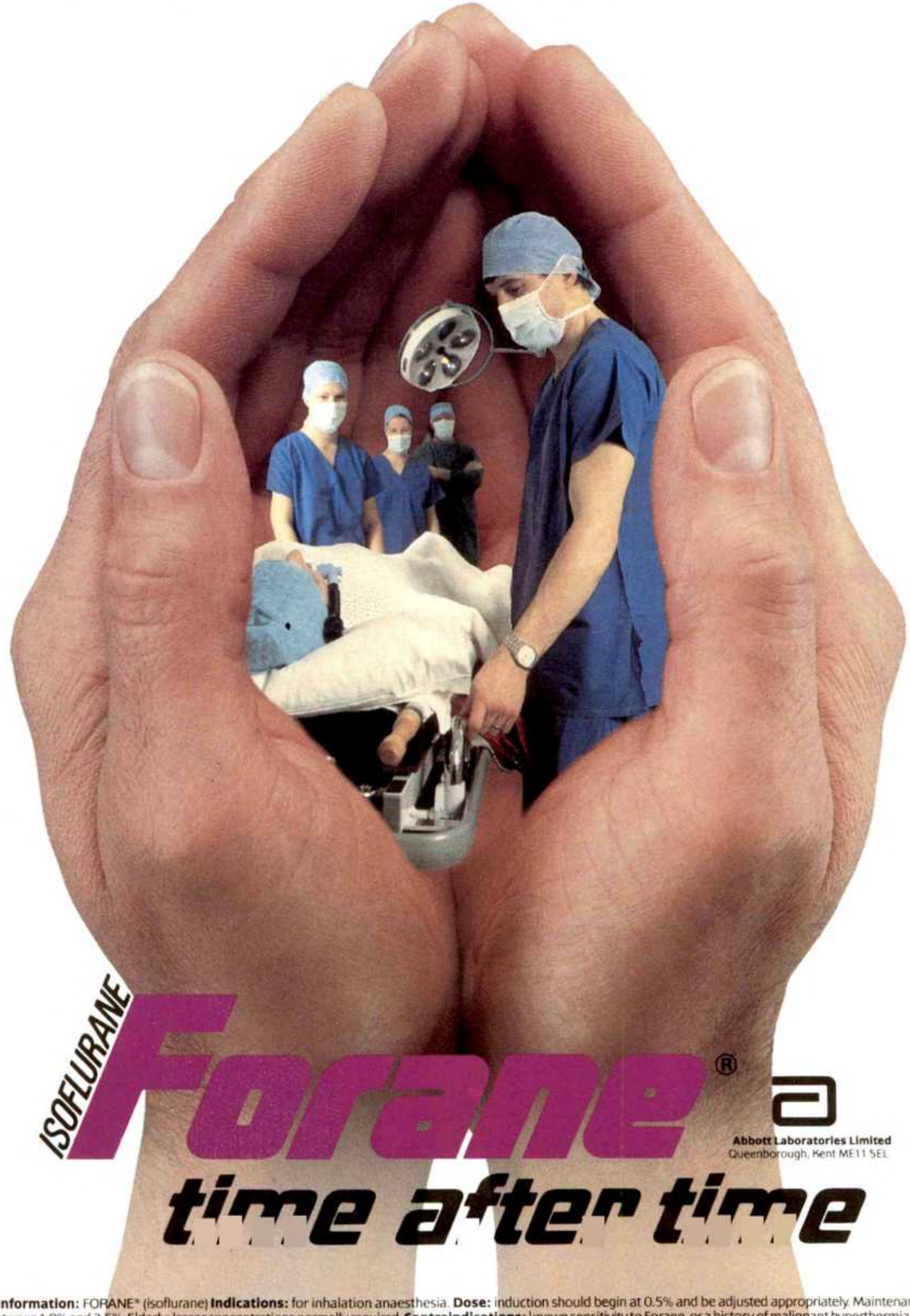

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 59, No. 5 MAY 1987

EDITORIAL

HALOTHANE IN THE DOLDRUMS

It is more than a year since the U.K. Committee on Safety of Medicines (CSM) first intimated to the Association of Anaesthetists and to the Faculty of Anaesthetists that its recommendation on the minimum interval between two halothane anaesthetics was to change from 28 days to 3 months. To many objective observers, the ensuing events are bizarre and deeply worrying.

CSM operates a national system to record and monitor suspected adverse drug reactions. Its previous activities in relation to halothane hepatotoxicity are well known. Reports of alleged halothane hepatotoxicity for the period 1964–78 were analysed by Inman and Mushin (1978). Of 251 cases considered, 82% involved multiple exposures to halothane and 75% of these multiple exposures involved at least two halothane anaesthetics within 28 days. Irrespective of the interval, multiple exposure was associated with a higher death rate (51%) than was single exposure (35%). On the basis of these findings, CSM recommended that repeated halothane anaesthesia should be avoided within 28 days, if possible. As with other epidemiological studies of halothane hepatotoxicity, the report did not establish the entity and the 28-day recommendation was nothing other than a cautious guess, there being many factors that were beyond control (Spence, 1986).

In a broadsheet issued last September (Committee on Safety of Medicines, 1986) it was announced that, between 1978 and 1985, 84 further reports of alleged hepatotoxicity associated with halothane had been received; in only 62 of these was the history adequate to allow further analysis. Twenty-one of the 62, of whom six died (29%), had received halothane only once. Of the remaining 41, 15 had received halothane twice within 28 days; nine had received it three or more times with unspecified intervals. Five of the nine (56%) died, compared with 13 (41%) of the 32 patients who had received halothane twice irrespective of interval; there is no indication of the number of deaths in the 15 patients who had been exposed twice within 28 days.

The figures may not be reliable, because CSM depends on a system of open reporting. It could be argued that the problem has been either under-reported or over-reported—or that under-reporting has been more marked for the 1978–85 period, since the total of such cases appears to be diminishing. The report by Inman and Mushin (1978) was silent on the step taken to "confirm" the role of halothane in liver damage—that is to exclude other factors (infection, enzyme inducers, known hepatotoxic drugs and hypoxia). It is well known, however, that CSM has no effective mechanism for such enquiry.

If the figures are reliable, they show that three or four patients have died annually from halothane hepatitis in the 7-year period 1978–85 compared with nine or 10 per year in the preceding 14 years. Among those who received halothane only once, the average annual deaths amounted to one and three, respectively.

If that were the whole story the solution would be to abandon halothane. Any death associated with anaesthesia is unacceptable, and appropriate steps should be taken to prevent it. However, that is not the whole story. It can be estimated that at least 500 anaesthetic deaths occur in the U.K. each year. Some are clearly not attributable to the drugs used. In others (circulatory failure, aspiration pneumonitis and other pneumonias, acute asphyxia) the contribution of drugs and techniques is much less clear. Neither do we have reliable information on the contribution of anaesthetic drugs to postoperative death from causes such as myocardial infarction and thrombosis and thromboembolism. Thus we feel our way in the dark and it is all too easy for science to give way to rhetoric.

The CSM pronouncement of last September recommended also that a careful anaesthetic history should be taken to determine previous exposure and previous reactions to halothane. It is usually easy to establish or assume a previous exposure, but a "previous reaction" may be more difficult. The matter is not helped by a third recommendation: "A history of unexplained jaundice or pyrexia in a patient following exposure to halothane is an absolute contraindication to its future use in that patient."

This is hopelessly superficial. Pyrexia is, of course, a common feature of the postoperative period, irrespective of the anaesthetic used. In some cases of presumed halothane hepatotoxicity the writer has noted that the patient has suffered protracted and inappropriate nausea and vomiting, quite distinct from what is regarded as commonplace in the postoperative period. For the most part, the temperature chart has been a poor guide.

In its most recent action on halothane, CSM may consider that it has performed its statutory function appropriately. It may even draw comfort from the knowledge that, in North America, the popularity of halothane has diminished more than has been the case in Britain. There is also unusual behaviour on the part of at least one of the medical defence societies, who seem to imply that there have been out of court settlements in civil actions brought in relation to halothane hepatitis (Bennets, 1986), although one cannot find anyone in anaesthetic circles who has knowledge of these patients or the reasons for settlement, if such has been the case.

It would be inappropriate to offer a rearguard action in favour of a drug which was demonstrably more dangerous than alternatives. Halothane, however, is not in that position. A letter from 13 professors of anaesthesia (Adams, and 12 others, 1986) has attempted to restate the case for continuing with halothane in anaesthetic practice, pointing to the need for knowing the totality of risk associated with drugs and techniques as distinct from focusing on one aspect of toxicity of one agent, however rare.

The present issues have raised fundamental problems in relation to future anaesthetic practice. It would appear that the anaesthetic profession, which prides itself in its grasp of clinical pharmacology, is being dictated to by non-anaesthetists whose understanding of the balance of risks in anaesthetic practice is probably deficient by our standards. Worse than that, there appears to be a stubbon refusal on the part of CSM to enter discussion which might, with hindsight, have been very helpful to them in coming to a more balanced conclusion in the first place. Even now they seem unwilling to make their data available for detailed scrutiny by experts other than those in their own organization. There is really nothing new from the CSM 1986 statement as compared with the Inman and Mushin report of 1978. On the other hand, the climate has changed, with a greater readiness in society to resort to litigation against doctors. It would be naive to imagine that no-one in the CSM had considered the influence on medico-legal argument that their recent bare pronouncements would have.

Finally, anaesthesia is not a particularly lucrative field for drug developers, and we owe it to the pharmaceutical industry to have sensible and objective views in adopting or rejecting drugs. If, after 30 years of comparatively safe use, halothane disappears in a smear campaign based on rare reports of toxicity the nature of which has still not been fully defined, what hope is there of a fair passage for any of our drugs?

A. A. Spence

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SODIUM THIOSULPHATE DECREASES BLOOD CYANIDE CONCENTRATIONS AFTER THE INFUSION OF SODIUM NITROPRUSSIDE

P. V. COLE AND C. J. VESEY

SUMMARY

Plasma and red cell cyanide, and plasma thiocyanate, concentrations were measured in 30 patients undergoing elective nitroprusside-induced hypotension. One randomly selected group ($n = 15$)*, who received 0.21–0.70 mg kg*$^{-1}$ *over periods of 50–160 min, were given a bolus of sodium thiosulphate 10.6–38.5 mg kg*$^{-1}$ *immediately on cessation of the nitroprusside administration. The other group, who received infusions of 0.11–0.85 mg kg*$^{-1}$ *for periods of 59–197 min, received no antidote. Cyanide concentrations, expressed as a percentage of the immediate post-infusion values, were significantly lower in the treated group in all subsequent blood samples (at 10, 30 and 60 min; plasma cyanide* $P < 0.05$*; red cell cyanide* $P < 0.001$*). Improved cyanide metabolism was further demonstrated by a sharp increase in mean plasma thiocyanate concentration* ($P < 0.05$) *in the group receiving the antidote.*

Widespread adherence to recommended maximum doses has virtually abolished reports of nitroprusside (SNP) toxicity (Verner, 1985). Despite this, we are consulted frequently about patients who have received the drug, most often as a long-term infusion, and who are giving cause for concern. After ascertaining whether the dose of SNP received by the patient could be a significant factor, we advise estimation of acid–base balance. If the patient is found to have a metabolic acidosis, we recommend the administration of sodium thiosulphate i.v. In our opinion, this drug is by far the most effective non-toxic cyanide antidote and, alone, has greatly increased the rate of cyanide detoxication when given as a bolus to dogs infused with high doses of SNP (Krapez et al., 1981; Vesey et al., 1985). We now report on its effectiveness when administered as a small bolus injection immediately after a period of nitroprusside-induced hypotension.

PATIENTS AND METHODS

Thirty patients undergoing major elective orthopaedic, vascular or plastic surgical procedures for which induced hypotension was normal practice were allocated randomly to two groups (table I). Each subject gave informed consent to blood sampling during anaesthesia. The two groups received sufficient SNP by controlled infusion to maintain the mean arterial pressure between 50 and 60 mm Hg during surgery. Immediately the infusion was stopped one group received a bolus dose of sodium thiosulphate (< 3 ml of a 50% solution). The dose of antidote was calculated for each individual patient immediately before its administration, and was about 50 times the weight of SNP infused (that is, 12 times the molar equivalent of its potential cyanide yield). Arterial blood samples were taken into iced heparinized syringes before infusion, immediately before the injection of the thiosulphate, and 10, 30 and 60 min later. They were transferred quickly to the laboratory in ice and water and centrifuged at 0 °C. The cyanide (HCN) in the plasma and saline-washed red cells was isolated by an aeration technique and measured by an autoanalytical procedure (Vesey and Cole, 1985), which was also

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TABLE I. *Summary of patient details (mean (SEM))*

	Smokers	Sex	Age (yr)	Wt (kg)	Total dose (mg)	SNP Infusion Dose (mg kg^{-1})	SNP Infusion Time (min)	SNP Infusion Dose rate (µg kg^{-1} min^{-1})	Thiosulphate dose (mg kg^{-1})
Controls (n = 15)	3	8F 7M	41.1 (4.1)	67.7 (3.9)	24.5 (3.7)	0.36 (0.06)	98.7 (12)	3.89 (0.51)	0
Antidote (n = 15)	8	8F 7M	39.1 (4.5)	67.0 (3.0)	30.2 (3.3)	0.45 (0.04)	88.9 (6.7)	5.43 (0.72)	25 (2.5)
t			0.33	0.16	1.14	1.27	0.73	1.76	
P			0.75	0.87	0.26	0.21	0.47	0.09	

used to measure the plasma thiocyanate (SCN) concentration (Vesey and Kirk, 1985).

The weights, age range and SNP dose and dose rate, and the percent changes in plasma and RBC HCN and plasma SCN concentrations for the two groups of patients were compared by a two-sample t test using the Minitab computer program (Pennsylvania State University, U.S.A.) (Ryan, Joiner and Ryan, 1976). Half-lives of plasma and red blood cell HCN concentrations were determined graphically.

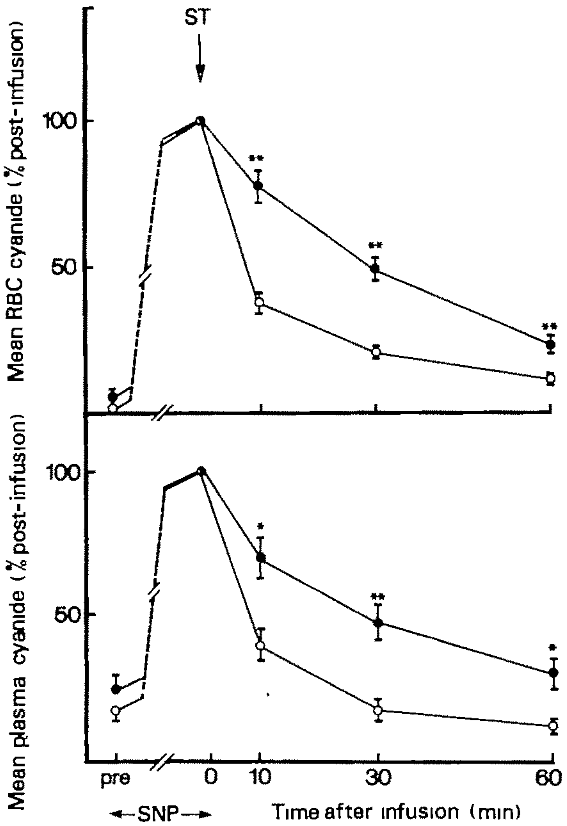

FIG. 1. Mean (±SEM) plasma and red cell cyanide concentrations, expressed as percentages of the immediate post-infusion values, in blood samples taken before, and after, SNP infusion, and 10, 30 and 60 min later. ○——○ = Patients receiving an injection of sodium thiosulphate (ST) 10.6–38.5 mg kg^{-1} immediately following infusion (n = 15). ●——● = Control group not given thiosulphate (n = 15). $^{*}P < 0.05$; $^{**}P < 0.001$.

RESULTS

The two groups of patients did not differ significantly with respect to age, sex and weight. Mean total doses and infusion rates of SNP were dissimilar but not significantly so (table I). The variation in individual doses resulted in wide differences in the immediate post-infusion plasma and erythrocyte HCN concentrations. The subsequent cyanide concentrations have, therefore, been expressed as percentages of the immediate post-infusion values (fig. 1); the absolute mean values are given in tables II and III. In addition, because only three patients in the control group were smokers compared with eight in the antidote group, base-line plasma SCN concentrations differed (table IV) although, once again, the

TABLE II. *Mean plasma cyanide concentrations (µmol litre^{-1}): control* v. *antidote*

	Sampling times (min) Pre.	Post.	+10	+30	+60
Controls					
Mean	0.12	0.58	0.44	0.29	0.16
SEM	0.02	0.90	0.08	0.06	0.03
n	15	15	15	15	14
Antidote					
Mean	0.15	0.95	0.36	0.14	0.11
SEM	0 03	0.12	0.05	0.03	0.02
n	15	15	15	15	15
t	0.77	2.49	0.89	2.47	1.25
P	0.45	0.02	0.38	0.02	0.22

TABLE III. *Mean red cell cyanide concentrations* (μ*mol litre*$^{-1}$)*: control* v. *antidote*

	Sampling times (min)				
	Pre.	Post.	+10	+30	+60
Controls					
Mean	0.9	40.7	34.2	23.3	8.6
SEM	0.2	8.1	7.6	6.4	2.0
n	15	15	15	15	14
Antidote					
Mean	0.7	88.3	33.7	19.4	10.5
SEM	0.12	15.0	5.7	3.5	1.7
n	15	15	15	15	15
t	0.91	2.74	0.05	0.54	0.72
P	0.37	0.01	0.96	0.59	0.48

TABLE IV. *Mean plasma thiocyanate concentrations* (μ*mol litre*$^{-1}$)*: control* v. *antidote*

	Sampling times (min)				
	Pre.	Post.	+10	+30	+60
Controls					
Mean	60.0	69.6	68.6	69.6	70.9
SEM	11.0	11.0	9.8	10.0	11.0
Antidote					
Mean	84.8	97.3	111.2	111.5	109.1
SEM	11.0	11.0	12.0	12.0	12.0
t	1.6	1.8	2.8	2.7	2.3
P	0.13	0.08	0.01	0.01	0.03

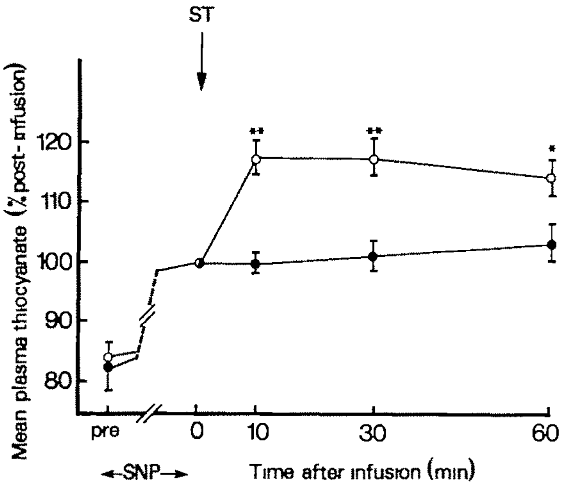

FIG. 2. Mean (±SEM) plasma thiocyanate concentrations, expressed as percentages of the immediate post-infusion values, in blood samples obtained before, and after, SNP infusion, and 10, 30 and 60 min later. ○——○ = Patients given a bolus injection of thiosulphate (ST) 10.6–38.5 mg kg^{-1} immediately after SNP infusion ($n = 15$). ●——● = Control group not receiving thiosulphate ($n = 15$). $^*P < 0.05$; $^{**}P < 0.001$.

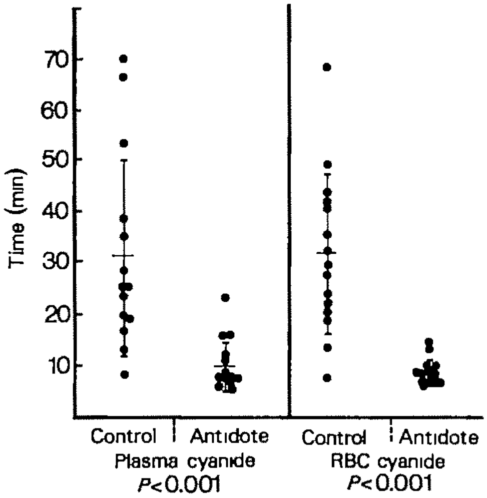

FIG. 3. Time taken for plasma cyanide and red cell cyanide concentrations to decrease by 50% following SNP administration (mean values). The antidote group received sodium thiosulphate 10.6–38.5 mg kg^{-1} immediately following the SNP infusion. $n = 15$ for both groups. Vertical bars represent SD.

differences did not achieve statistical significance. The SCN concentrations were also expressed as percentages of post-infusion values. Actual mean concentrations are presented in table IV.

The two groups showed highly significant differences in the percentage HCN and SCN concentrations at 10, 30 and 60 min after SNP infusion (figs 1 and 2). The estimated time intervals between the end of infusion and the point at which HCN concentrations decreased by 50% (T_{50}) are indicated in figure 3. This shows that thiosulphate significantly shortened T_{50} and reduced the scatter of results.

DISCUSSION

The detoxication of HCN to form the relatively non-toxic SCN$^-$ ion requires a source of sulphane sulphur (that is, divalent sulphur joined to one or more sulphur atoms). A number of compounds containing this combination, in particular thiosulphate and its organic derivatives, are normal products of metabolism arising from the amino acid cysteine. Several biochemical mechanisms can utilize these sulphur compounds to detoxicate HCN (Westley et al., 1983), but the most important is considered to be that catalysed by rhodanese (thiosulphate: cyanide sulphurtransferase, EC 2.8.1.1.), an enzyme present in the mitochondria and particularly abundant in liver and kidney. This enzyme will transfer sulphur from thiosulphate to a number of acceptor molecules including HCN. The abundance and wide distribution of rhodanese within the body indicates potential ability to detoxicate large quantities of cyanide (Himwich and Saunders, 1948)—something which is inconsistent with the surprisingly low lethal dose of HCN for man (< 50 mg) and the slow rate of detoxication demonstrated in patients infused with SNP (Vesey and Cole, 1985). This suboptimal activity of rhodanese is attributed to inadequate endogenous supplies of thiosulphate and to the low permeability of the mitochondrial membrane for this ion (Sorbo, 1975).

The enhancement of cyanide metabolism by increasing the supply of thiosulphate is illustrated in three ways by the results of this study. First, in spite of the higher mean HCN concentrations at the end of infusion in the antidote group, the plasma and red cell HCN concentrations at 10, 30 and 60 min were significantly lower than in the control group (fig. 1). Second, the formation of SCN was enhanced by the dose of thiosulphate. Whereas plasma SCN concentrations in the control group changed little over the course of 60 min, those in the antidote group increased abruptly, reaching a plateau 10 min after the end of the SNP infusion (fig. 2). Finally, mean T_{50} for both plasma and red cell concentrations of HCN in the antidote group were almost a quarter that in the control group (fig. 3). This demonstrates also a wide spread of detoxication rates amongst the control patients and suggests that some individuals may be at greater risk from HCN than others. However, the administration of the thiosulphate reduced this range markedly, indicating that body supplies of sulphane sulphur are the limiting factor, rather than inadequate rhodanese concentrations—as suggested by Davies and colleagues (1975). This action of thiosulphate mirrored the results reported previously for dogs (Vesey et al., 1985).

Our results indicate that the administration of sodium thiosulphate is an effective method of reducing plasma and red cell HCN concentrations after the infusion of SNP. Moreover, sodium thiosulphate is a safe drug—there are no recorded adverse effects except for a single report of dehydration after long-term infusion in dogs (Michenfelder and Tinker, 1977), and large doses can be given without toxic effect (Pasch, Schulz and Hoppelshäuser, 1983; Schulz, 1986). We believe that the other common antidotes should be reserved for massive cyanide poisoning; sodium nitrite and cobalt EDTA are toxic drugs (Kiese and Weger, 1969; Dodds and McKnight, 1985) unsuitable for use in patients who have received SNP.

Our recommended regimen for suspected SNP overdose is:

(1) Determine whether the total dose of SNP is greater than 1.5 mg kg^{-1} for short-period infusions, or the dose rate greater than 4 μg kg^{-1} min^{-1} for long-term infusions (Vesey, Cole and Simpson, 1976; Vesey and Cole, 1985).

(2) Assess acid–base balance; in particular, confirm the presence (or otherwise) of a metabolic acidosis.

(3) If a base deficit is present, administer: 50% sodium thiosulphate 25 ml by i.v. injection and correct the acidosis with sodium bicarbonate, as appropriate.

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EFFECT OF CISAPRIDE ON MORPHINE-INDUCED DELAY IN GASTRIC EMPTYING

D. J. ROWBOTHAM AND W. S. NIMMO

SUMMARY

Forty patients were allocated randomly to receive one of four premedications i.m.: placebo only, morphine 10 mg plus placebo, morphine 10 mg plus cisapride 10 mg and morphine 10 mg plus cisapride 4 mg. Gastric emptying after each premedication was assessed using the oral paracetamol absorption model. The morphine only group and the morphine and cisapride 4 mg group showed delayed gastric emptying when compared with the placebo group. Delay in gastric emptying in the morphine and cisapride 10 mg group was not demonstrated. It is concluded that cisapride 10 mg prevents the delay in gastric emptying associated with the administration of morphine.

Morphine and other opioids delay the emptying of the stomach and the absorption of orally administered drugs (Nimmo, Wilson and Prescott, 1975; Todd and Nimmo, 1983). Inhalation of gastric contents is an important cause of anaesthetic mortality (Lunn and Mushin, 1982), and the use of opioids before the induction of anaesthesia may increase this risk. Any agent which would prevent, or reverse, this delay in gastric emptying, without decreasing the analgesic effects of any administered opioid, would fulfill a useful role in anaesthesia.

Cisapride (R 51 619, Janssen Pharmaceuticals Ltd) is a gastric and intestinal pro-kinetic drug. It is a derivative of cis-4-amino-3-methoxypiperidine and is currently undergoing clinical trials in the U.K., U.S.A., Germany, France, Belgium and Australia. Applications for product licences in these countries are to be made shortly.

In man, cisapride increases lower oesophageal sphincter pressure (Corazziari, Bontempo and Anzini, 1984), increases the rate of gastric emptying, and reduces the mouth-to-caecum transit time (Baeyens, Reyntgens and Verlinden, 1984). It is devoid of any stimulatory or inhibitory effects on the composition of gastric acid and on its basal volume (Reyntgens et al., 1984).

The purpose of this study was to investigate the effect of cisapride on gastric emptying in patients after premedication with morphine.

PATIENTS AND METHODS

Forty patients (36 male), aged 18–64 yr, who were about to undergo surgery were studied. Local ethics advisory committee approval and informed patient consent were obtained. No patient had any evidence of gastrointestinal disease; none was taking any medication that would affect this system. Patients who could possibly be pregnant were excluded.

Patients were allocated randomly to receive, in a double-blind fashion, one of four premedications i.m.: group 1 = placebo only; group 2 = morphine 10 mg plus placebo; group 3 = morphine 10 mg plus cisapride 10 mg; group 4 = morphine 10 mg plus cisapride 4 mg.

Both cisapride preparations represented 2 ml of solution and the placebo was physiological saline 2 ml. The premedication was given into the right thigh using a 23-s.w.g. needle, 2 h before surgery.

Following premedication gastric emptying was assessed using the rate of absorption of orally administered paracetamol (Nimmo, Wilson and Prescott, 1975; Todd and Nimmo, 1983). Paracetamol 1.5 g (three tablets) was taken with water 50 ml, 20 min after the injection of the premedication. Venous blood was obtained before the administration of the premedication, and then

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every 15 min for 90 min after the paracetamol. Plasma paracetamol concentrations were determined by high pressure liquid chromatography (Howie, Adriaenssens and Prescott, 1977). Samples for the analysis of cisapride were taken at the same times and were analysed by high pressure liquid chromatography.

The rate of paracetamol absorption was estimated by the area under the plasma concentration–time curve (AUC) at 45, 60 and 90 min. Statistical analysis of these values, and of the paracetamol concentrations, was by Student's *t* test after logarithmic transformation of the data.

The peak paracetamol concentrations, and the time to achieve that peak, were compared between the groups using the Student's *t* test and the Mann–Whitney *U* test, respectively.

The groups were tested for significant differences, in respect of age, sex and weight, using the Chi-squared test and Student's *t* test.

Cisapride concentrations in groups 3 and 4 were compared using Student's *t* test.

Any adverse effects of the drug, especially nausea and vomiting, were noted.

RESULTS

There were no statistical differences between the groups with respect to age, sex and weight (table I).

No serious adverse effects were noted. One patient in group 4 complained of slight nausea for a short time, 50 min after the premedication of morphine 10 mg plus cisapride 4 mg. No patient vomited.

The mean paracetamol concentrations in the four groups are shown in figure 1 and table II.

There were significantly higher plasma paracetamol concentrations in the placebo group when compared with the morphine only group at 45, 60, 75 and 90 min ($P < 0.05$). At these times, there were also significantly higher concentrations in the morphine plus cisapride 10 mg group when compared with the morphine only group ($P < 0.05$). There was no difference between the morphine plus cisapride 10 mg group and the placebo only group. After cisapride 4 mg, paracetamol concentrations did not differ from those in the morphine only group.

TABLE I. *Patient characteristics (mean ± SD)*

	Sex	Age (yr)	Weight (kg)	Type of operation	
Group 1	10 M	46±16	77±10	General surgery	(6)
(n = 10)	0 F			ENT	(3)
				Orthopaedic	(1)
Group 2	10 M	46±14	76±11	General surgery	(5)
(n = 11)	1 F			ENT	(5)
				Orthopaedic	(1)
Group 3	8 M	47±10	74±11	General surgery	(8)
(n = 10)	2 F			ENT	(1)
				Orthopaedic	(1)
Group 4	8 M	36±17	80±13	General surgery	(5)
(n = 9)	1 F			ENT	(3)
				Orthopaedic	(1)

TABLE II. *Plasma paracetamol concentrations* ($\mu g\ ml^{-1}$) *(mean ± SEM)*. $P < 0.05$: * *Compared with group 1*; † *compared with group 2*

	15 min	30 min	45 min	60 min	75 min	90 min
Group 1 (n = 10)	17.0±5.2	17.0±3.4	18.0±1.9	15.9±1.2	15.5±1.2	16.0±2.2
Group 2 (n = 11)	6.8±2.7	10.2±2.9	8.9±2.0*	10.2±1.5*	10.9±1.3*	10.8±1.0*
Group 3 (n = 10)	7.3±3.3	17.1±3.3	16.4±2.0†	14.7±1.3†	14.2±1.2†	13.6±1.2†
Group 4 (n = 9)	5.7±3.0	9.8±3.8	9.3±2.6	10.7±2.7	10.9±2.6	10.1±2.2

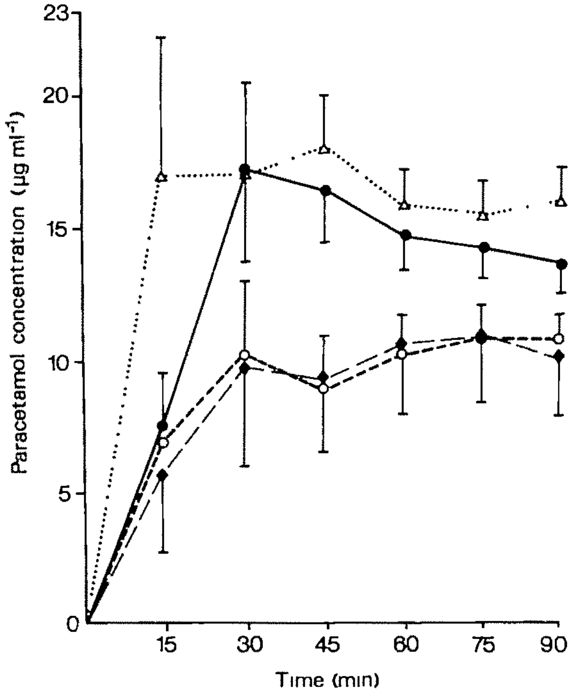

FIG. 1. Paracetamol concentrations (mean ± SEM). △...△ = Group 1; ○—○ = group 2; ●——● = group 3; ◆-·-·-◆ = group 4.

TABLE III. *Areas under the plasma concentration time curves (AUC) ($\mu g\ ml^{-1}$ min) at 45, 60 and 90 min (mean ± SEM).* $P < 0.05$: * *Compared with group 1;* † *compared with group 2*

	AUC 45	AUC 60	AUC 90
Group 1 ($n = 10$)	644 ± 129	897 ± 132	1369 ± 137
Group 2 ($n = 11$)	322 ± 95*	466 ± 114*	787 ± 114*
Group 3 ($n = 10$)	493 ± 81†	726 ± 91†	1151 ± 102†
Group 4 ($n = 9$)	304 ± 125	452 ± 151	771 ± 214

TABLE IV. *Peak paracetamol concentrations ($\mu g\ ml^{-1}$) and times to achieve peak concentrations (min) (mean ± SEM).* * $P < 0.01$ *compared with group 1;* † $P < 0.05$ *compared with group 2*

	Peak concn	Time of peak
Group 1	28.6 ± 3.2	39.0 ± 12.3
Group 2	14.6 ± 2.0*	57.3 ± 17.3
Group 3	22.6 ± 3.2†	51.0 ± 16.1
Group 4	13.7 ± 3.5	70.0 ± 23.3*

The AUC obtained in the four groups at 45, 60 and 90 min are shown in table III.

The AUC 45, 60 and 90 min were significantly less in the morphine only group when compared with the placebo only group ($P < 005$). The AUC 45, 60 and 90 were significantly greater in the morphine plus cisapride 10 mg group when compared with the morphine only group ($P < 0.05$), but were not significantly different when the morphine plus cisapride 10 mg group was compared with the placebo only group. After morphine plus cisapride 4 mg, the AUC did not differ from those in the morphine only group.

The peak paracetamol concentrations, and the times to achieve these peaks, are shown in table IV.

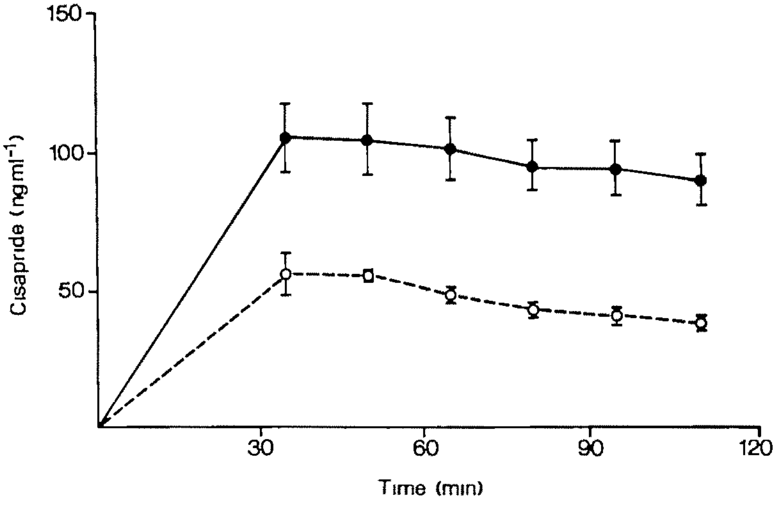

FIG. 2. Cisapride concentrations (mean ± SEM). ●——● = Group 3; ○---○ = group 4.

There was a significantly lower peak paracetamol concentration in the morphine only group when compared with the control group ($P < 0.01$). Peak concentrations were significantly greater in the morphine plus cisapride 10 mg group when compared with the morphine only group ($P < 0.05$). Cisapride 4 mg failed to achieve this effect.

The time to peak concentrations showed a trend towards a delay in the morphine only group when compared with the control group and a reduction in the delay in the morphine plus cisapride 10 mg group. However, these differences failed to achieve statistical significance. There was a significant delay in the time to achieve peak concentrations in the morphine plus cisapride 4 mg group when compared with the control group ($P < 0.01$).

The mean plasma cisapride concentrations for groups 3 and 4 are shown in figure 2. The cisapride concentrations at every time were significantly greater in the cisapride 10 mg when compared with the cisapride 4 mg group ($P < 0.01$).

DISCUSSION

Morphine delayed the absorption of paracetamol presumably by inhibiting gastric emptying, as paracetamol is absorbed only after leaving the stomach. The addition of cisapride 4 mg to the morphine failed to prevent this delay. Similarly, metoclopramide 10 mg i.m. has been found to be ineffective in reversing the delay in gastric emptying caused by diamorphine and pethidine using the same methodology (Nimmo, Wilson and Prescott, 1975).

Cisapride, in a dose of 10 mg i.m., prevented the delay in gastric emptying caused by morphine. This larger dose of cisapride was well tolerated by the patients and, in particular, no extrapyramidal side-effects were noted. This is to be expected as cisapride has been shown to be devoid of any anti-dopaminergic action (Reyntgens et al., 1984).

The plasma cisapride concentrations show evidence of good absorption after i.m. administration and significantly greater concentrations of cisapride in the cisapride 10 mg group than in the 4 mg group.

No conclusions can be made as regards to the incidence of preoperative nausea and vomiting with cisapride as the numbers in this trial were too small. This question would be of importance if cisapride were to be used routinely with morphine as a premedication.

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EFFECT OF ANXIETY ON GASTRIC EMPTYING IN PREOPERATIVE PATIENTS

K. H. SIMPSON AND A. F. STAKES

SUMMARY

On the morning of operation 30 patients awaiting minor gynaecological surgery completed a Spielberger State Trait Anxiety Inventory. Gastric emptying was then measured using paracetamol absorption. Anxiety State scores, which reflected situational anxiety, were unrelated to Anxiety Trait scores, which assessed anxiety proneness. Paracetamol absorption was reduced and delayed in patients with low anxiety trait who developed high anxiety state before surgery, compared with patients whose anxiety state scores were lower than, or similar to, their anxiety trait scores. Therefore, it was concluded that gastric stasis occurred in patients with a low predisposition to anxiety who became apprehensive whilst awaiting surgery.

Pulmonary aspiration of gastric contents remains an important cause of anaesthetic mortality and morbidity (Lunn and Mushin, 1982), and many studies have demonstrated the presence of large volumes of acid stomach contents in patients prepared for surgery. For example, Hester and Heath (1977) recovered more than 40 ml of fluid from the stomach of one in eight patients presenting for elective surgery—despite prolonged fasting. In over half the patients, the pH of the gastric contents was less than 2.5. More than 25 ml of acidic stomach fluid was aspirated from 66% of patients presenting for minor outpatient operations (Ong, Palahniuk and Cumming, 1978).

It has been suggested that pain and anxiety cause gastric stasis, but few studies have attempted to differentiate these factors. However, it is known that trauma to the extremeties in the dog, and cold stress in man, may reduce gastric motility (Zaricznyj et al., 1977; Thompson, Richelson and Malagelada, 1982). In 1983 Marsh, Spencer and Nimmo measured gastric emptying in 10 patients 2–3 h before elective surgery, and again 2–5 days later, to assess the effect of preoperative anxiety. As there was no difference in paracetamol absorption on the two occasions, it was concluded that anxiety had no effect on gastric emptying, although anxiety was not quantified as it was assumed to be present in all preoperative patients.

When studying anxiety it is important to distinguish between temporary emotional states and stable personality dispositions. Cattel and Scheier (1958) applied multivariate factor analysis techniques to the definition and measurement of anxiety; state and trait anxiety consistently emerged as principal personality dimensions. Anxiety state increased in stressful situations, and was defined as "a transitory emotional condition or feeling, characterised by subjective, consciously perceived tension and apprehension with heightened autonomic nervous system activity". Anxiety trait is anxiety proneness, defined as "a stable long range predisposition to respond to stress with anxiety, and the tendency to perceive a wide variety of situations as threatening". In 1970, Spielberger, Gorsuch and Lushene developed the State–Trait Anxiety Inventory to provide a reliable, brief, self-reporting questionnaire to measure both facets of anxiety. The anxiety state scale increased in response to various kinds of stress and decreased after training in techniques promoting relaxation (Spielberger, 1975). It correlated well with other measures of situational anxiety such as the Multiple Affect Adjective Checklist (Zuckerman, 1960). The anxiety trait scale correlated with other measures of anxiety predisposition such as the Taylor Manifest Anxiety Scale (Taylor, 1953) or the Institute for Personality and Ability Testing (IPAT) scale (Cattel and Scheier, 1958).

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Johnston (1980) used the Spielberger questionnaire to study the natural course of perioperative apprehension and showed that anxiety was not restricted to the immediate preoperative period; only a small proportion of patients reached maximum anxiety on the day of surgery. The present study was designed to measure preoperative anxiety and anxiety proneness, as well as gastric emptying.

PATIENTS AND METHODS

On the morning of operation 30 fit patients awaiting minor gynaecological surgery completed a Spielberger State Trait Anxiety Inventory, which gave a numerical score, out of 80, for anxiety state and trait. Gastric emptying was then measured using a paracetamol absorption technique similar to that described by Heading and colleagues in 1973. After a fast of at least 4 h an indwelling i.v. cannula was sited in a forearm vein under local anaesthesia. Paracetamol 1.5 g with 150 ml of water was given by mouth. Patients remained supine for 2 h whilst blood was sampled at intervals; plasma was frozen at −20 °C for paracetamol assay as a batch.

Paracetamol was measured using an enzymatic assay method, specific for the parent compound, which did not detect paracetamol metabolites (Cambridge Life Sciences). The enzyme aryl acylamide amidohydrolase was used to split the amide bond of paracetamol, producing acetate and p-aminophenol. The latter reacted with o-cresol to form a stable blue compound which was measured using a spectrophotometer capable of reading at 615 nm. The procedure was automated to improve the performance of the assay at the low concentrations of paracetamol expected.

The area under the plasma paracetamol concentration–time curve was calculated using the trapeziodal rule. Data were analysed using Pearson's Product Moment Correlation Coefficient, multiple regression analysis, Student's t test or one-way analysis of variance for independent samples.

RESULTS

The anxiety state and anxiety trait scores of the 30 women were not significantly correlated ($r = 0.31$, $t = 1.75$). Multiple regression analysis showed that gastric emptying was delayed in patients with a low anxiety trait who developed a high anxiety state, compared with those whose anxiety state was lower than, or similar to, their anxiety trait. To give a numerical value for the level of preoperative apprehension relative to anxiety predisposition, each patient's anxiety trait score

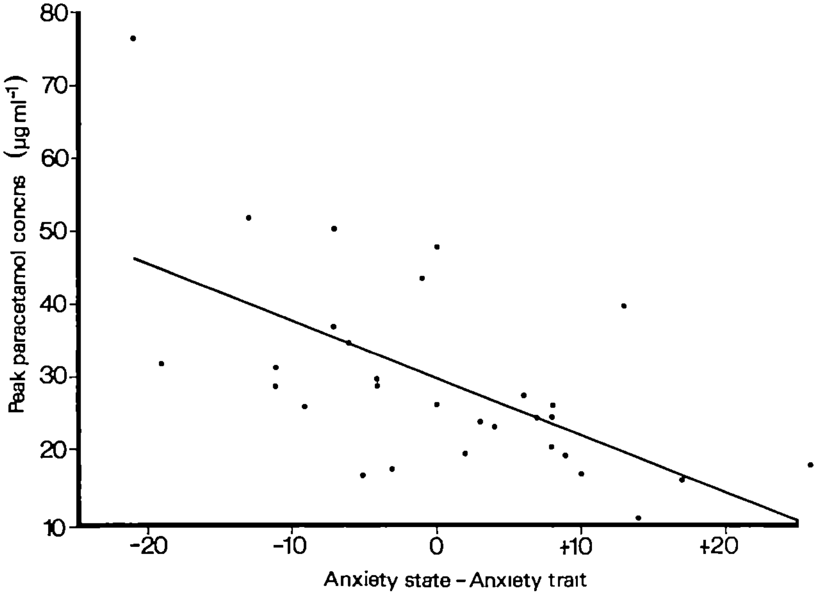

FIG. 1. Relationship between peak plasma paracetamol concentrations and difference between anxiety state and anxiety trait scores (AS–AT). Regression equation: $y = 30.1 - 0.8x$; $r = -0.61$; $t = 4.07$; $P < 0.005$.

was subtracted from their anxiety state score. Linear regression of peak plasma paracetamol concentration against the difference between the anxiety scores demonstrated a significant relationship ($P < 0.005$). Peak paracetamol concentrations decreased as anxiety state increased relative to anxiety trait (fig. 1).

Patients were grouped according to the relationship between anxiety state and anxiety trait scores. In 16 patients anxiety state was less than or equal to anxiety trait, and in 14 patients anxiety state was greater than anxiety trait. The ages, weights and duration of fasting in the two groups were not significantly different (table I).

TABLE I. *Age, weight and duration of fasting in the two groups (Anxiety State = AS; Anxiety Trait = AT)*

	Age (yr)	Weight (kg)	Starved (h)
AS $\leqslant$ AT (n = 16)			
Mean	26.6	60.2	5.7
SEM	2.5	3.3	0.9
AS > AT (n = 14)			
Mean	28.3	59.6	7.9
SEM	2.9	2.6	1.2

Mean plasma paracetamol concentrations were significantly lower at 15, 30 ($P < 0.01$), 45 and 60 ($P < 0.05$) min in patients with a low anxiety trait who developed a high anxiety state before surgery (fig. 2). These patients also had significantly reduced and delayed peak paracetamol concentrations ($P < 0.005$) (table II).

TABLE II. *Peak plasma paracetamol concentrations and time to peak (Anxiety State = AS; Anxiety Trait = AT)* * P < *0.005*

	Peak paracetamol concentration (μg ml^{-1})	Time to peak (min)
AS $\leqslant$ AT (n = 16)		
Mean	36.3	35.6
SEM	3.8	6.0
AS > AT (n = 14)		
Mean	21.9*	64.3*
SEM	1.8	8.0

Patients with a high anxiety state relative to anxiety trait had a smaller area under the plasma paracetamol concentration–time curve during the first 1 h, and over the 2 h of the study ($P < 0.005$) (fig. 3).

DISCUSSION

The use of the Spielberger State Trait Anxiety Inventory permitted evaluation of situational anxiety and anxiety predisposition in patients awaiting surgery. The finding that anxiety trait was not predictive of preoperative anxiety state was in agreement with previous work. It has been shown that stressful situations of an ego-threatening nature evoke greater increase in anxiety state in subjects with a high anxiety trait

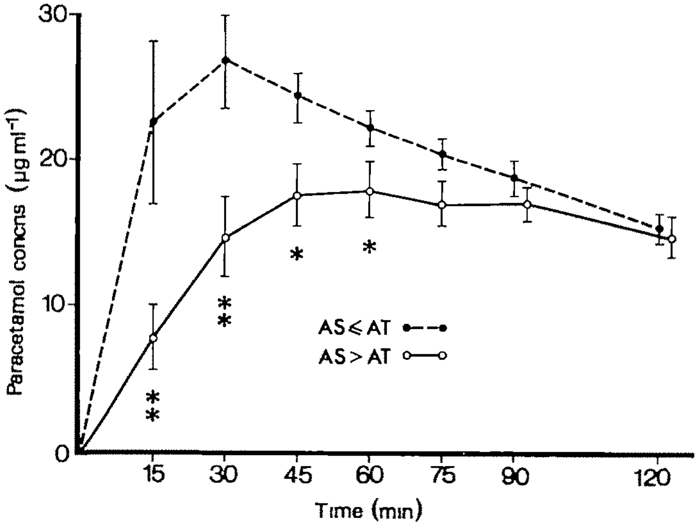

FIG. 2. Mean plasma paracetamol concentration at each time. Anxiety state = AS; anxiety trait = AT. **$P < 0.01$; *$P < 0.05$.

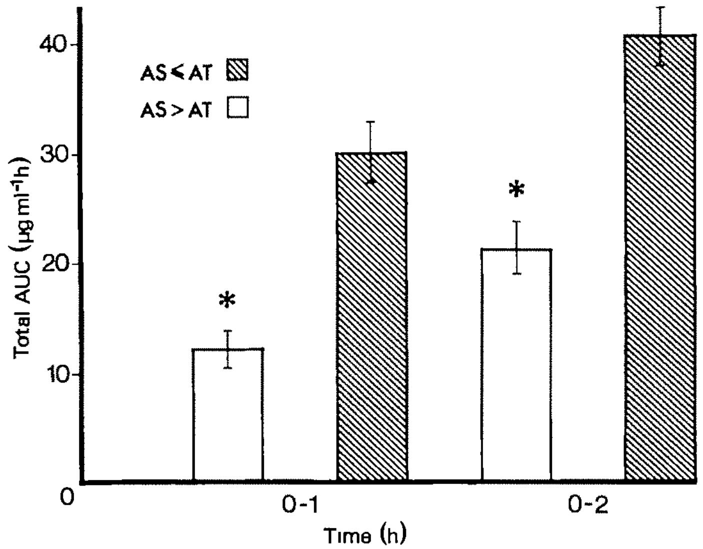

FIG. 3. The area under the plasma paracetamol concentration–time curve (AUC), over 1 and 2 h. Anxiety state = AS; anxiety trait = AT. $^{*}P < 0.005$.

(Auerbach, 1973a). However, in circumstances involving physical danger, including surgery, the magnitude of the change in anxiety state is unrelated to anxiety trait (Johnson, Dabbs and Leventhal, 1970; Auerbach, 1973b; Spielberger et al., 1973).

Heading and colleagues (1973) showed a significant negative correlation between the half-time of gastric emptying and peak plasma paracetamol concentrations ($r = -0.77$). Therefore, the decrease in peak paracetamol concentrations seen in patients with high anxiety state, relative to anxiety trait, represented a delay in gastric emptying. The smaller area under the plasma paracetamol concentration–time curve in these patients reflected a slowing of paracetamol absorption. Therefore, gastric stasis was demonstrated in patients who had a low predisposition to anxiety who became very anxious in the preoperative period. Patients with high anxiety proneness did not show any delay in gastric emptying, whatever their anxiety state score. These subjects may have been tolerant of frequent high levels of anxiety.

Perhaps gastric motility was altered by neural or endocrine mechanisms in the anxious patients. The beta-adrenergic system has been shown to exert an inhibitory action on gastric emptying in normal circumstances (Rees et al., 1978); isoprenaline decreases and propranolol increases stomach emptying (Clark et al., 1980). Corticosteroids and adrenaline, in physiological concentrations, increase the amount of acidity of gastric secretions (Gray et al., 1951; Chaikof et al., 1961; Christensen and Stadil, 1976). The role of endocrine factors on changes in gastric motility in anxious patients merits further study.

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EVALUATION OF THE COMBINED EFFECTS OF GLYCOPYRROLATE AND NEOSTIGMINE ON THE LOWER OESOPHAGEAL SPHINCTER

M. C. DERRINGTON, N. HINDOCHA AND G. SMITH

SUMMARY

The effects on the lower oesophageal sphincter (LOS) of the simultaneous administration of glycopyrrolate 0.5 mg and neostigmine 2.5 mg, when given to antagonize neuromuscular blockade, were studied in 10 healthy patients undergoing gynaecological surgery. LOS pressure and gastric pressure (GP) were measured for 20 min after the administration of the drug combination and barrier pressure (BrP) was calculated (LOS – GP). There was a significant reduction in BrP which lasted, in some patients, for the duration of the study. These results contrast with those of a similar study looking at the effects of atropine and neostigmine in which the decrease in BrP, although significant, was transient, and in which control values were regained after 5 min.

The intrinsic tone of the lower oesophageal sphincter (LOS) represents the major barrier to gastro–oesophageal reflux. The barrier pressure (BrP) represents the pressure gradient which opposes reflux and it is calculated by subtracting gastric pressure (GP) from LOS pressure. In view of the importance of regurgitation to the anaesthetist, there have been many investigations of the effects of anaesthetic drugs and techniques on BrP in recent years.

On a previous occasion, we examined the effects of a combination of atropine 1.2 mg and neostigmine 2.5 mg on BrP and demonstrated that a significant reduction occurred (Turner and Smith, 1985). This was evident soon after the administration of the drugs. Although this is a potentially deleterious effect, it is probably not important clinically because it was short-lived. There has been increasing use of glycopyrrolate instead of atropine and, because of its relatively long duration of action, we have investigated the effects of glycopyrrolate 0.5 mg and neostigmine 2.5 mg (Klingenmaier et al., 1972) under the same circumstances as in our previous study.

PATIENTS AND METHODS

Twelve healthy patients undergoing elective intra-abdominal gynaecological surgery gave informed consent to take part in this study, which was approved by the District Ethical Committee. The subjects were free from gastrointestinal, respiratory or cardiovascular disease, were not receiving any medication and, where appropriate, had refrained from smoking for the 8 h before the induction of anaesthesia.

The same anaesthetic technique was used as in our previous study (Turner and Smith, 1985): premedication with diazepam 0.2 mg kg^{-1} by mouth 2 h before operation, induction with thiopentone 4 mg kg^{-1}, and pancuronium 0.1 mg kg^{-1} to facilitate tracheal intubation and artifical ventilation (minute ventilation of 100 ml kg^{-1}). Anaesthesia was maintained with 70 % nitrous oxide and 0–1 % enflurane in oxygen with morphine sulphate for analgesia.

The oesophageal manometry tube (Gaeltec Ltd) was connected via a preamplifier to a multichannel chart recorder (Linear Recorder Mk III). In brief, it contains three small pressure transducers 5, 10 and 15 cm from its tip, is calibrated in a water column before use and again at the end of the study, and has insignificant calibration or baseline drift over periods exceeding

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90 min and with temperature variations of 1–2 °C. A full description of the apparatus and method of measurement by "pull through" manoeuvre may be found in previous publications from this department (Turner and Smith, 1985; Cotton and Smith, 1981; Cotton and Smith, 1984). Pull through manoeuvres in which all three transducers pass from stomach through the lower oesophageal sphincter to oesophagus are made at end expiration and show sequential measurements of these pressures on the channels from each transducer in turn. Artefacts such as coughs and swallows can be distinguished as they are recorded from each transducer simultaneously. The barrier pressure is calculated from the measurements of gastric pressure and lower oesophageal sphincter pressure. In the present study three control measurements were taken during stable anaesthesia before the antagonism of residual neuromuscular blockade. After the administration of neostigmine 2.5 mg and glycopyrrolate 0.5 mg, measurements were taken every 1 min for 20 min, during which time anaesthesia was maintained with 70% nitrous oxide and 0–2% enflurane in oxygen to prevent the patient straining or coughing.

All the results were assessed statistically using analysis of variance followed by Student's t test for paired data, comparing each minute with control. A comparison with those of the previous study was made to assess whether the atropine–neostigmine sequence or the glycopyrrolate–neostigmine sequence had the more marked effect on BrP.

RESULTS

After the administration of glycopyrrolate and neostigmine, all except one of the patients showed a biphasic response in BrP over the period of 20 min. After an inconsistent and very brief decrease, there was a sharp increase and then a prolonged decrease. The pressure changes did not occur at exactly the same time in each patient, but there was a statistically significant ($P < 0.05$) reduction in BrP by 8 min which was sustained throughout the period of study. From a control value of 27.2 cm H_2O ± 3.4 (SEM) BrP decreased to 18.8 cm H_2O ± 1.3 at 8 min and remained low, reaching 16.1 cm H_2O ± 1.3 at 20 min—the end of the study period (fig. 1). These results contrast with those of the previous study in which, after the administration of atropine 1.2 mg and neostigmine 2.5 mg, the potentially deleterious effect of the atropine was rapidly negated by the neostigmine such that by 3 min the net effect on LOSP and BrP was negligible. Table I shows a comparison of the lowest values of BrP reached in the two studies, this value as a percentage of control BrP, and the time at which this occurred.

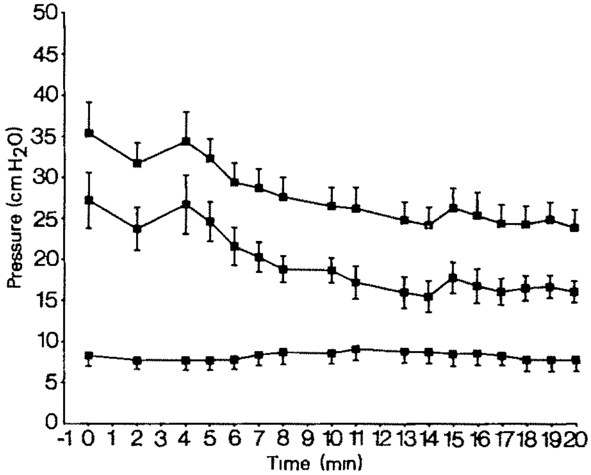

FIG. 1. Effect of the simultaneous administration of glycopyrrolate 0.5 mg and neostigmine 2.5 mg on LOS pressure (upper profile), BrP (middle profile) and GP (lower profile) (mean ± SEM). $n = 12$.

TABLE I. *Comparison of time to lowest value of BrP, actual lowest value of BrP reached and lowest value as a percentage of control value between atropine 1.2 mg and neostigmine 2.5 mg (A–N) and glycopyrrolate 0.5 mg and neostigmine 2.5 mg (G–N) (mean ± SEM)*

	BrP Lowest value (cm H_2O)	Lowest value (% control)	Time to lowest value (min)
A–N	13.7 ± 1.7	51.7 ± 2.7	3.2 ± 0.7
G–N	12.7 ± 1.2	50.1 ± 4.8	12.8 ± 1.6

DISCUSSION

It is generally believed that the resting tone in the lower oesophageal sphincter is the major barrier to gastro–oesophageal reflux (Cohen and Lipshutz, 1971). The variable which is important in preventing reflux is not the LOS tone itself, but the pressure difference between the LOS and the stomach and this is referred to as the barrier pressure. It is not possible to define a barrier pressure below which all patients exhibit gastro–oesophageal reflux, although a correlation has been demonstrated between reflux (utilizing oesophageal pH testing) and yield barrier pressure (Haddad, 1970). It is, therefore, suggested that a reduction in barrier pressure is likely to be associated with an increased tendency to regurgitation (Cotton and Smith, 1984). This has been confirmed by a study of the effect of hyoscine and atropine on the lower oesophageal sphincter in volunteers. Brock-Utne and colleagues (1977) demonstrated, in 16 healthy volunteers devoid of gastrointestinal disease, that both atropine 0.6 mg and hyoscine 0.4 mg, produced decreases in barrier pressure of the order of 10 cm H_2O, which led to reflux being demonstrable on straining in 25% of the subjects. This suggests that a relatively moderate reduction in barrier pressure may be associated with an increased tendency to reflux.

Normally, there is an adaptive reflex increase in LOS pressure to an increase in intra-abdominal pressure, thus preventing reflux (Lind, Warrian and Wankling, 1966). It has been shown that this adaptive response is diminished following the administration of atropine (Lind, Crispin and McIver, 1968), and it is also decreased in pregnant women at term who have symptoms of reflux (Lind et al., 1968).

Thus, the effects on the LOS, of drug and drug combinations used during general anaesthesia, may be important, particularly if these effects have a long duration of action. It has been reported previously (Turner and Smith, 1985) that antagonism of neuromuscular blockade with atropine and neostigmine did cause a significant decrease in barrier pressure, but this effect was transient.

In the present study, a combination of glycopyrrolate 0.5 mg and neostigmine 2.5 mg was shown to cause a significant reduction in barrier pressure of 50% (of the order of 10 cm H_2O) which, by analogy with the study of Brock-Utne and colleagues (1977) might be expected to be associated with reflux on straining in some patients. Furthermore, the significant reduction in barrier pressure lasted for as long as 20 min in some patients. The deleterious effects of the combination of neostigmine and glycopyrrolate on the LOS may, therefore, still be present once the trachea has been extubated, and the patient returned to the recovery area or the general surgical ward.

A control group was not included in the present study since previous studies from this Department have demonstrated that, over the duration of this study, and with the techniques used, there is no significant variation in barrier pressure with time (Cotton, Smith and Fell, 1981). Furthermore, our previous study on the effect of atropine and neostigmine on the lower oesophageal sphincter (Turner and Smith, 1985) showed that barrier pressure demonstrated only a transient decrease in a group of patients undergoing the same type of surgery under identical anaesthetic conditions.

The results suggest that when glycopyrrolate and neostigmine are given simultaneously in the standard clinical doses, the patient may be at increased risk of regurgitation from decreases in barrier pressure. This drug combination should probably be avoided in situations where regurgitation is likely, and our previous study suggests that the combination of atropine and neostigmine is preferable.

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PHARMACOKINETICS OF MIDAZOLAM IN TOTAL I.V. ANAESTHESIA

P. PERSSON, A. NILSSON, P. HARTVIG AND A. TAMSEN

SUMMARY

The pharmacokinetics of midazolam during total i.v. anaesthesia were determined in 15 female patients undergoing major surgery. Midazolam was administered together with an analgesic drug and a neuromuscular blocking drug. The dose regimen of midazolam, based on simulations, included two consecutive infusions following a bolus injection at the induction of anaesthesia. Multiple blood samples were drawn and a two-compartment open model was fitted to the measured plasma concentrations. Plasma clearance (483 ml min^{-1}), apparent volume of distribution (1.94 litre kg^{-1}) and terminal half-life (3.1 h) were in agreement with other reports. Thus, there was no obvious evidence that the surgical procedure or the concomitant use of other drugs, or both, influenced the pharmacokinetics of midazolam. The relatively rapid elimination makes midazolam suitable for use by infusion in a total i.v. technique.

Total i.v. anaesthesia, defined as anaesthesia provided solely by drugs administered i.v. has, until now, played a minor role in the provision of anaesthesia for major surgery. However, an awareness of the problems associated with nitrous oxide (Chanarin, 1980; Brodsky, 1983; Mazze, 1983; Wolf, Capuano and Hartung, 1983) has lead to an increased interest in this technique.

Midazolam is a benzodiazepine with a short elimination half-life and a relatively short duration of action (Greenblatt et al., 1981; Smith, Eadie and O'Rourke Brophy, 1981). At physiological pH midazolam is un-ionized and lipophilic. As a result the onset of action after i.v. administration is rapid because of rapid uptake by the brain. An understanding of the kinetics of midazolam under the conditions pertaining during surgery, and a knowledge of the plasma concentration required to produce an hypnotic effect are essential when designing a total i.v. technique. Theoretically, the short elimination half-life of midazolam, and the negligible hypnotic effect of its metabolites (Crevoisier et al., 1983; Ziegler et al., 1983), make the administration of midazolam by i.v. infusion potentially useful.

The objectives of the present study were: to construct a dose regimen, based on simulations; to determined the pharmacokinetics of midazolam in total i.v. anaesthesia during major surgery; and to compare the simulated and the observed concentration–time profiles.

PATIENTS, MATERIALS AND METHODS

Patients

Fifteen female patients scheduled for elective hysterectomy were included in the study. Their ages varied from 36 to 53 yr and their body weights were between 45 and 88 kg (mean (±SD) 66±11 kg) (table I).

The study was approved by the Ethics Committee of the Medical Faculty of Uppsala University, and informed consent was obtained from each patient.

Premedication and anaesthetic procedure. Pethidine 75 mg and atropine 0.5 mg were given i.m. as premedication. Anaesthesia was induced and maintained with midazolam (and alfentanil) as follows:

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TABLE I. *Body weight, total duration of infusion, total dose of midazolam and area under the concentration–time curve (AUC) in 15 female surgical patients*

Patient No.	Weight (kg)	Duration of infusion (min)	Total dose (mg)	AUC (mg min^{-1} litre^{-1})
1	45	120	31	81.7
2	58	90	36	59.4
3	72	105	47	117.6
4	70	75	42	89.7
5	63	75	38	96.8
6	53	75	32	62.7
7	66	90	41	82.2
8	81	75	48	82.6
9	88	75	52	67.0
10	64	75	38	77.0
11	66	75	36	79.2
12	65	75	35	77.7
13	67	75	36	90.9
14	76	75	41	89.7
15	56	75	30	80.6
Mean	66	82	39	82.2
±SD	11	14	6	14.4

Patients 1–10: a bolus injection of midazolam 0.3 mg kg^{-1} was followed by an infusion regimen with an initial infusion rate of 0.68 mg kg^{-1} h^{-1} for 15 min followed by a maintenance infusion of 0.125 mg kg^{-1} h^{-1};

Patients 11–15: a bolus dose of midazolam 0.25 mg kg^{-1} followed by an initial infusion of 0.65 mg kg^{-1} h^{-1} for 15 min and a maintenance infusion of 0.13 mg kg^{-1} h^{-1}.

The mean (± SD) total duration of infusion was 82 ± 14 min, corresponding to a total dose of midazolam of 31–52 mg (table I).

In patients 1–5 analgesia was provided by the administration of alfentanil as a bolus dose (0.05 mg kg^{-1}) followed by an infusion (0.06 mg kg^{-1} h^{-1}) and additional increments of alfentanil were given when indicated. Patients 6–15 were given a bolus dose of 0.075 mg kg^{-1} followed by a two-stage infusion of alfentanil 0.3 mg kg^{-1} h^{-1} for 15 min followed by 0.0625 mg kg^{-1} h^{-1} for as long as the midazolam infusion was maintained. Atracurium 0.5 mg kg^{-1} (patients 1–5) or pancuronium 0.1 mg kg^{-1} (patients 6–15) was given to provide neuromuscular blockade before intubation of the trachea. The lungs were ventilated with oxygen in air during the surgical procedure. At the end of surgery residual neuromuscular blockade was antagonized with neostigmine 2.5 mg (plus atropine 1.0 mg).

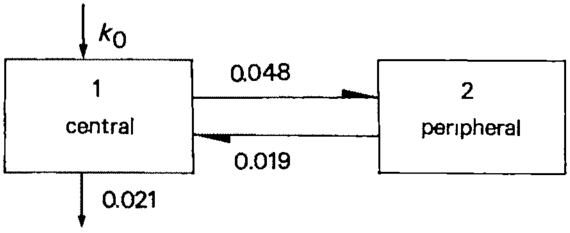

FIG. 1. A two-compartment open model for midazolam used for the simulations. The rate constants (min^{-1}) were taken from the literature (Lauven et al., 1981). k_0 represents the infusion rates.

Intraoperative and postoperative observations. Arterial pressure, heart rate and pupil size were monitored during anaesthesia. Any evidence of lachrymation, sweating, or both was noted. End-tidal carbon dioxide concentration, EMG, EEG and train-of-four response were recorded (Datex ABM-monitor (Nilsson and colleagues, 1986; unpublished observations)).

The patient's ability to give their name and date of birth and to solve simple arithmetic problems (addition and subtraction of two-figured numbers) in the postoperative period were recorded.

Blood sampling and assay. Blood samples were drawn from a peripheral vein before and 2, 5, 10 and 15 min after induction. Thereafter, samples were collected every 15 min until the end of the infusion. Following the termination of the infusion, samples were drawn at 2, 5, 10, 15, 30 and 60 min and then every 1 h for 6 h. The blood was centrifuged and the plasma frozen at −20 °C pending analysis.

Plasma concentrations of midazolam were determined by gas chromatography using nickel-63 electron capture detection (Rutherford, 1977). Linear standard curves for the concentration range of midazolam 10–1000 ng ml^{-1} were obtained.

Design of midazolam infusion regimens

The dose of midazolam received by the first 10 patients was derived from published pharmacokinetic data obtained following a single bolus dose (table II). A two-compartment open model was assumed (fig. 1) and a continuous simulation program (DARE-P) (Wait and Clarke, 1974) was used to simulate an infusion regimen. After a bolus dose of 0.3 mg kg^{-1} a two-stage infusion regimen was constructed. The rapid loading infusion rate was determined after numerous simulations using the two-compartment model. The maintenance

TABLE II. *Pharmacokinetic data of midazolam used in the simulation. Pharmacokinetic data determined in six female patients undergoing minor gynaecological surgery (Lauven et al., 1981)*

	Mean	Range
Total plasma clearance (ml min^{-1})	472	380–527
Volume of the central compartment (litre kg^{-1})	0.40	0.26–0.53
Apparent volume of distribution (litre kg^{-1})	1.72	1.38–2.27
Distribution half-life (min)	8.6	7.0–11.1
Elimination half-life (h)	2.5	2.2–2.8

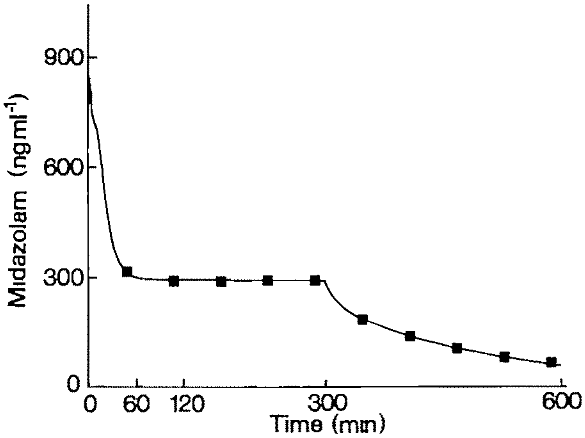

FIG. 2. Simulated concentration–time profile for midazolam after two consecutive infusion rates combined with a bolus injection. The bolus injection was 0.3 mg kg^{-1}, while the infusion rates were 0.68 mg kg^{-1} h^{-1} for 15 min followed by 0.125 mg kg^{-1} h^{-1} over the next 285 min.

infusion was calculated from the equation (Rowland and Tozer, 1980):

$$k_0 = Cl \cdot C^{ss} \qquad (1)$$

where k_0 was the maintenance infusion rate, Cl was the total plasma clearance and C^{ss} the desired steady-state concentration.

In patients 1–10 this infusion regimen was theoretically expected to result in a steady-state concentration of 300 ng ml^{-1} from 45 min onwards (fig. 2), a value which has been found to provide adequate sedation during surgery (Nilsson, Tamsen and Persson, 1986).

The infusion regimen for patients 11–15 was based on the results obtained in patients 1–10. Theoretically, the aim of this regimen was to give a steady-state concentration of midazolam 250 ng ml^{-1} from 45 min onwards.

Data analysis

The differential equations (Appendix) were fitted to the individual plasma concentration–time data by the non-linear least square regression program DARE-MINUIT (University of Uppsala, Uppsala, Sweden). The data points were given different weights (equal, $1/y$) to obtain the best fit.

The pharmacokinetics of midazolam were calculated using the equations given in the Appendix.

Statistical analysis

Mean values and standard deviations were calculated using standard equations. All data are presented as mean ± SD. Comparison between groups was made with Student's t test. A P-value < 0.05 was considered significant.

Linear regression was used to evaluate the relationship between the pharmacokinetics and body weight: correlation coefficients were calculated according to Pearson (Colton, 1974).

RESULTS

Pharmacokinetics

The relationships between mean plasma midazolam concentrations and time, for the two patient groups (1–10 and 11–15) are shown in figure 3. The mean initial concentrations, 2 min after the bolus dose, were 1254 ± 626 ng ml^{-1} in patients 1–10 and 919 ± 272 ng ml^{-1} in patients 11–15. These values were not significantly different ($P > 0.05$). The mean concentrations at the end of the infusion were 317 ± 74 ng ml^{-1} (range 192–405 ng ml^{-1}) in the first group and 375 ± 48 ng ml^{-1} (range 335–443 ng ml^{-1}) in the second group of patients ($P > 0.05$).

The simulated concentration, 2 min after the bolus dose, was 52% lower than the mean observed concentration. At the end of the infusion this difference was 6% in patients 1–10, compared with 47% in patients 11–15. The simulated concentrations, 30 min after the end of the infusion, were 14% higher in patients 1–10 and 22% lower in patients 11–15.

The best individual fit to the pharmacokinetic data following i.v. infusion was obtained by a

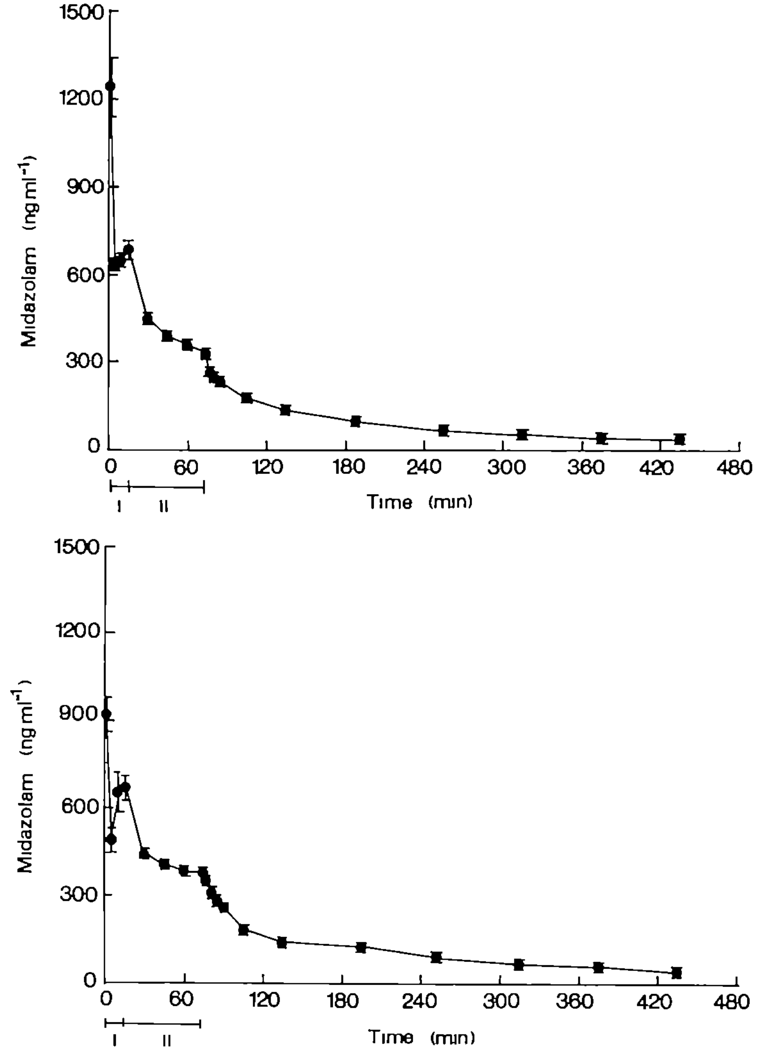

FIG. 3. Observed midazolam plasma concentrations for patients 1–10 (top) and for patients 11–15 (bottom). Mean values ± SEM. I and II represent the duration of the first and the second infusion, respectively.

two-compartment open model (fig. 1). The resulting fit to the data for one patient is shown in figure 4. The mean values of the calculated rate constants are shown in table III.

The total plasma clearance (*Cl*) of midazolam was 483 ± 109 ml min^{-1}, range 372–788 ml min^{-1}. After correction for body weight the variations in clearance ranged between 5.55 and 10.46 ml min^{-1} kg^{-1}. The mean clearance in patients 1–10 was 512 ml min^{-1} compared with 426 ml min^{-1} in patients 11–15.

The apparent volume of distribution (Vd^{β}) for midazolam also showed a two-fold variation (1.35–2.83 litre kg^{-1}) with a mean of 1.94 ± 0.55 litre kg^{-1}. This resulted in a mean terminal elimination half-life ($T_{\frac{1}{2}}^{\beta}$) of 3.1 h (range 2.0–4.9 h) while the mean half-life for the distribution phase ($T_{\frac{1}{2}}^{\alpha}$) was 18 min. The volume

TABLE III. *Mean values of the calculated rate constants of midazolam in 15 surgical patients*

	k_{10} (min^{-1})	k_{12} (min^{-1})	k_{21} (min^{-1})
Mean	0.0175	0.0185	0.0098
± SD	0.0063	0.0083	0.0031

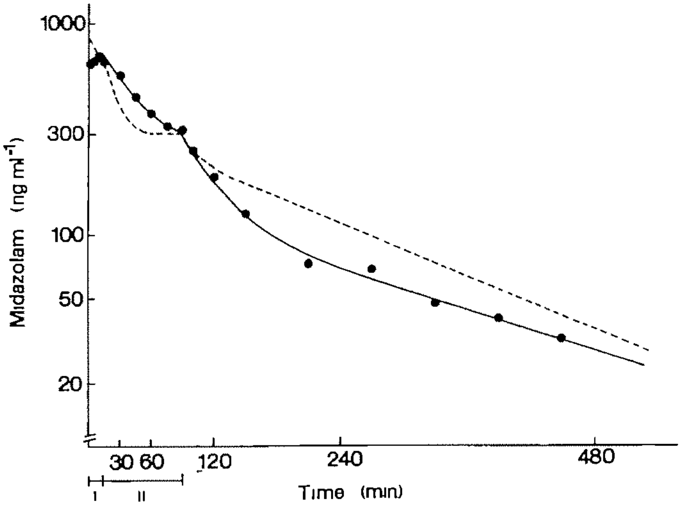

FIG. 4. Midazolam plasma concentrations for patient No. 7. The straight line represents the fit; the broken line represents the simulated concentrations. I = Initial infusion; II = maintenance infusion.

of the central compartment was 0.471 litre $kg^{-1} \pm 0.131$. The individual pharmacokinetic parameters are presented in table IV.

There was a good correlation between body weight and the total apparent volume of distribution ($r = 0.72$; $P < 0.01$) with a tendency towards a proportionate increase in volume of distribution even after correction for body weight ($r = 0.428$; $P > 0.05$) (fig. 5). Furthermore, there was a weak correlation between the elimination half-life and increasing body weight ($r = 0.567$; $P < 0.05$). On the other hand, total clearance (*Cl*) did not change significantly with increasing body weight ($r = -0.288$; $P > 0.05$).

The mean blood loss during the investigation was around 300–500 ml (includes surgery and blood sampling).

Correlation between performance and plasma concentration

The mean plasma concentration of midazolam at the time of extubation was 166 ± 38 ng ml^{-1}.

TABLE IV. *Individual pharmacokinetic parameters of midazolam in 15 surgical patients: total plasma clearance* (Cl), *volume of the central compartment* (V_1), *apparent volume of distribution* (Vd^{β}), *distribution half-life* ($T_{\frac{1}{2}}^{\alpha}$) *and the elimination half-life* ($T_{\frac{1}{2}}^{\beta}$)

Patient No.	*Cl* (ml min^{-1})	V_1 (litre kg^{-1})	Vd^{β} (litre kg^{-1})	$T_{\frac{1}{2}}^{\alpha}$ (min)	$T_{\frac{1}{2}}^{\beta}$ (h)
1	379	0.479	1.48	16	2.0
2	607	0.328	1.95	9	2.2
3	400	0.325	1.44	16	3.0
4	468	0.456	2.83	22	4.9
5	392	0.453	1.40	23	2.6
6	510	0.401	1.95	13	2.4
7	498	0.482	2.19	24	3.4
8	581	0.514	2.62	26	4.2
9	788	0.575	2.71	13	3.5
10	493	0.774	2.81	28	4.2
11	455	0.335	1.57	18	2.6
12	450	0.697	1.75	18	2.9
13	396	0.346	1.62	12	3.2
14	457	0.430	1.35	21	2.5
15	372	0.468	1.43	16	2.5
Mean	483	0.471	1.94	18	3.1
±SD	109	0.131	0.55	6	0.8

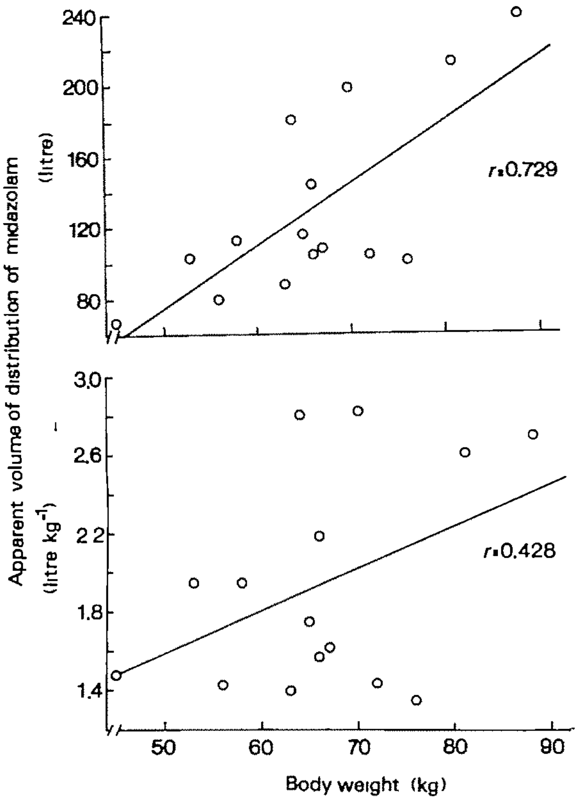

FIG. 5. Correlation of total body weight to midazolam volume of distribution ($V\mathrm{D}^{\beta}$) (expressed both with and without correction for total body weight). Solid lines were determined by linear regression analysis.

Mean time from extubation until the patient was able to give her name and date of birth was 76±62 min; mean plasma concentration of midazolam at this time was 104±38 ng ml^{-1}. The ability to solve simple arithmetic problems was established at 89±63 min after extubation; the corresponding plasma concentration of midazolam was 96±42 ng ml^{-1}.

DISCUSSION

Drugs administered i.v. in anaesthetic practice are usually characterized by a rapid onset, and a short duration, of action. For most agents, the short duration of action results from a rapid decrease in plasma concentration as a result of extensive redistribution from brain to poorly-perfused tissues. However, when an infusion is administered i.v. at a constant rate, the total body clearance of the drug determines the steady-state plasma concentration, and the terminal elimination half-life has an important influence on the duration of action after the discontinuation of the infusion.

When considering the pharmacodynamic and pharmacokinetic properties of drugs in total i.v. anaesthesia, account has to be taken of the various factors which can influence the action of the drugs, such as the hepatic blood flow, protein binding and the drug metabolizing capacity of the patient as well as the concomitant use of other drugs. Knowledge of the plasma concentration required for hypnotic or analgesic effects as well as reliable pharmacokinetic data are also essential.

Pharmacokinetics of midazolam

A three-compartment model for midazolam has been proposed (Smith, Eadie and O'Rourke Brophy, 1981; Avram, Fragen and Caldwell, 1983). However, a biexponential elimination gave the best fit to the individual data in this study, and the midazolam kinetics obtained were similar to those reported by others. The mean total plasma clearance of 483 ml min^{-1} was similar to those found in healthy volunteers (Greenblatt et al., 1984; Smith, Eadie and O'Rourke Brophy, 1981) and in surgical patients (Lauven et al., 1981; Avram, Fragen and Caldwell, 1983; Harper et al., 1985). Changes in hepatic blood flow during surgery may influence total body clearance. However, the clearance values found in the present study did not differ from those reported from studies in healthy volunteers—indicating a negligible influence of surgery.

The apparent volume of distribution ($V\mathrm{D}^{\beta}$) of midazolam obtained in the present study (1.94 litre kg^{-1}) was comparable to those in previous studies (Lauven et al., 1981; Smith Eadie and O'Rourke Brophy, 1981; Harper et al., 1985). The tendency towards an increasing volume of distribution with increasing body weight (fig. 5) indicates that the bolus injection and loading infusion should be relatively higher in obese patients. On the other hand, there was no indication for a different maintenance infusion in these patients, since the plasma clearance did not depend on body weight. The influence of body weight on midazolam disposition is consistent with the findings of others for midazolam (Greenblatt et al., 1984), and for other lipophilic benzodiazepines such as diazepam (Abernethy and Greenblatt, 1982).

The infusion regimen

This study was based on the assumption that the hypnotic effect of midazolam is correlated with its plasma concentration (Allonen, Ziegler and Klotz, 1981; Aaltonen et al., 1985). Compared with midazolam, the main metabolite α-hydroxy midazolam has less hypnotic activity and a shorter elimination half-life (Crevoisier et al., 1983; Ziegler et al., 1983), indicating that a continuously maintained plasma concentration of midazolam should give a stable therapeutic effect without cumulation. In a previous study, a plasma concentration of midazolam of around 300–400 ng ml^{-1} was found to produce satisfactory anaesthesia during major surgery when used in combination with fentanyl (Nilsson, Tamsen and Persson, 1986).

The time taken to attain a steady-state plasma concentration is dependent upon the half-life of the drug. Approximately 90% of the steady-state concentration will be attained after three half-lives, that is about 9 h for midazolam. However, in a two-compartment system (as for midazolam) the time to reach the steady-state plasma concentration depends on the fraction of the total area (AUC) associated with the terminal phase. If this fraction is small, then the time to reach a plasma steady-state will be governed mainly by the distribution half-life ($T_{\frac{1}{2}}^{\alpha}$). However, for midazolam the terminal half-life will primarily determine the time to reach a steady-state plasma concentration, since the terminal phase represents the major part of the total area. To achieve a steady-state concentration more rapidly, a bolus dose was combined with a two-stage infusion regimen.

There are several possible approaches to designing an infusion regimen (Wagner, 1974; Schwilden et al., 1983). The advantage of the present method is that the high initial concentration produced a relatively rapid onset of action. It is an advantage to have a relatively high concentration of the anaesthetic drug at the moment of intubation and at the beginning of surgery, and the high therapeutic index (Pieri et al., 1981) of midazolam did not contraindicate this method. Prolonged infusion will not, with the present infusion strategy, result in an increasing plasma concentration of midazolam. This is important, since a high concentration at the end of surgery could lead to marked postoperative sedation.

The dose regimen calculated from simulations in a two-compartment model indicated a constant concentration of midazolam from 45 min onwards (fig. 2). In some patients, however, a steady-state concentration was not achieved during the infusion. The main reason for the discrepancy between simulated and observed data in these patients is probably the assumption of instantaneous equilibrium within each compartment in the simulation model. In reality, the distribution process within each compartment might have been slower. This is probably the explanation of the fact that the observed concentration, 2 min after the bolus dose, was significantly higher than the simulated concentration. Moreover, the relatively short period of infusion was probably insufficient to establish steady-state conditions. However, there is a tendency to a plateau phase (fig. 3) with reasonably good correlations with predicted values, although there were rather large interindividual differences.

Midazolam is almost completely metabolized in the liver—indicating an intermediate value of hepatic extraction ratio of midazolam. Thus, the clearance of midazolam depends on the metabolic capacity of the liver, the fraction of unbound midazolam and the hepatic blood flow (Rowland, Benet and Graham, 1973; Wilkinson and Shand, 1975). Interindividual differences in these indices may influence the concentration at, and the time to achieve, steady-state. In fact, the interindividual variability in the pharmacokinetics was greater in the present study than in the study by Lauven and colleagues (1981) (table II; table IV).

Patients 1–10 showed a slightly higher plasma clearance than had initially been assumed. Patients 11–15 had their infusion regimen modified based on the results from these first 10 patients. The aim of the modified regimen was to decrease the steady-state value and, thereby, decrease postoperative sedation. However, the steady-state value achieved in patients 11–15 did not differ from that in the first 10 patients, most probably as a result of the fact that patients 11–15 had a lower mean plasma clearance than patients 1–10. On the other hand, the peak values were reduced.

Concentration and effect of midazolam after infusion

The initial decrease in the plasma concentration of midazolam after the termination of the infusion was rapid, from about 350 ng ml^{-1} to 150 ng ml^{-1} in 1 h. Clinically, these values correspond to an anaesthetized patient and to a patient responding to verbal stimuli in the postoperative period, respectively. This rapid decline is partly the result of metabolism and partly the result of the continuous re-distribution of midazolam from the central to the peripheral compartment. Following this rapid phase, however, the decline in plasma concentration is slower, the patients often drifting back into sleep when undisturbed. This phase lasts for several hours, indicating that midazolam is being released slowly from the peripheral compartment.

The data demonstrated a relatively good correlation between the plasma concentrations of midazolam and postoperative sedation, despite the variations in the alfentanil plasma concentrations (Persson and colleagues, 1986; unpublished observations). Concentrations of midazolam in excess of 50–75 ng ml^{-1} signify postoperative drowsiness.

When simulated and observed plasma concentrations are compared, a tendency is seen for the simulated concentration to be lower during the infusion and higher after the termination of the infusion. This could partly be explained, as mentioned above, by the fact that a steady-state condition was not achieved during the investigation. After the termination of the infusion this would result in a greater distribution from the central to the peripheral compartment than that predicted by the simulation. After the infusion, distribution will have less influence than elimination on the plasma concentration decay with time. Theoretically, this implies that the duration of the hypnotic effect and hence, postoperative sedation, might be more pronounced after the infusion, than following a single i.v. bolus.

CONCLUSION

This investigation showed that, during surgery and in combination with the opioid drug alfentanil, midazolam showed a pharmacokinetic behaviour not unlike that previously reported from studies in healthy volunteers. We believe that the predictable, and relatively rapid, elimination of midazolam (and the low hypnotic activity of its metabolites) make midazolam a suitable hypnotic for use in a total i.v. technique.

APPENDIX

Midazolam kinetics after the infusion regimen are described by differential equations according to a two-compartment model (fig. 1):

Change of the amount of drug (A_1) with time in the central compartment:

$$dA_1/dt = R_{inf} - k_{10} \cdot A_1 - k_{12} \cdot A_1 + k_{21} \cdot A_2$$

where R_{inf} = rate of infusion (mg min^{-1}).

Change of the amount of drug (A_2) with time in the peripheral compartment:

$$dA_2/dt = k_{12} \cdot A_1 - k_{21} \cdot A_2$$

The resulting concentration–time profile in the central compartment (C_1) was obtained by the following relationship.

$$C_1 = A_1/V_1$$

where V_1 = volume of central compartment (l).

The disposition rate constants (α and β) were estimated from the fractional rate constants:

$$k_{10} = \frac{\alpha \cdot \beta}{k_{21}}$$

$$k_{12} = \alpha + \beta - k_{21} - k_{10}$$

The total plasma clearance (Cl) and the apparent volume of distribution ($V\text{D}^{\beta}$) were calculated from:

$$Cl = \frac{\text{Total dose}}{\text{AUC}}$$

$$V\text{D}^{\beta} = \frac{Cl}{\beta}$$

The area under the concentration–time curve (AUC) was calculated by the trapezoidal rule. The residual area beyond the last sampling point to infinity was determined from the calculated concentration at the final sampling time divided by the terminal slope (β).

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MIDAZOLAM SEDATION FOLLOWING OPEN HEART SURGERY

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Midazolam, a water-soluble benzodiazepine, with a short elimination half-life (1.5–3 h) and absence of clinically important hypnotically active metabolites, is a suitable agent with which to produce sedation in the intensive care unit. Short term ventilatory support is practised widely following open heart surgery (Peters, Bruin and Utley, 1979) and, because of its more favourable pharmacokinetic profile, midazolam has been shown to be preferable to diazepam when used in repeated intermittent doses in this situation (Lowry et al., 1985). Cumulation was less with midazolam, with little risk of a prolonged hypnotic effect following the discontinuation of its administration. However, because of the short elimination half-life, frequent small doses of midazolam are required to maintain a plasma concentration adequate for sedation while avoiding large swings in concentration after each administration. In spite of the low temperatures (25 °C) used during cardiac operations, the liver is well able to handle the midazolam presented to it, as clearance has been shown to be adequate in patients after cardiopulmonary bypass (Harper et al., 1985). Infusions of midazolam should, therefore, be a safe way of providing sedation during ventilatory support after open heart surgery. This paper presents the plasma concentrations obtained when midazolam 2.0 mg was administered hourly and compares these with the concentration obtained when the same dose was given as a continuous infusion.

SUMMARY

Midazolam given as hourly intermittent injections was compared with the same dose given by infusion for postoperative sedation in patients after cardiopulmonary bypass. A stable concentration was rapidly attained with the infusion whereas 6–8 h was required to attain stable plasma (trough) concentrations in the intermittent injection group. Plasma concentrations decreased rapidly to low values within 6 h of discontinuation of therapy. High plasma concentrations and a long (16 h) half-life were noted in one patient who may be a slow metabolizer of the drug.

PATIENTS AND METHODS

Twenty adult patients requiring ventilation following open heart surgery were studied. Those with hepatic dysfunction (noted on routine biochemical screening), receiving concurrent benzodiazepine therapy or with a history of hypersensitivity to benzodiazepines were excluded. Anaesthesia was induced with fentanyl 50 μg kg^{-1}, and maintained with air–oxygen supplemented, if necessary, with halothane. No benzodiazepines were given during the operative procedure. Neuromuscular blockade was produced with pancuronium 0.1 mg kg^{-1}.

Once in the cardiac recovery ward, all patients received a loading dose of midazolam 2 mg and they were then randomly allocated to receive either 2 mg at 1-h intervals or a continuous infusion of 2 mg h^{-1}. Both therapies were delivered via the internal jugular vein. Both groups were given morphine 2 mg i.v., as required, when there was evidence (lachrymation, tachycardia) that the sedation was too light.

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Samples of arterial blood (5 ml) were drawn before midazolam was administered and at 7.5, 15, 30, 60, 120 min and 4, 6, 8, 10, 12 h after the initial dose. In the intermittent injection group the blood was drawn immediately before a supplementary dose, thus reflecting the minimum (trough) concentration. At 4, 8 and 12 h further samples were drawn 10 min after administration, reflecting near-peak concentrations.

Another sample was taken before the discontinuation of the infusion at approximately 06.00 h the following morning, and also before and 10 min after the last intermittent injection. Further blood was drawn at 2, 4, 6, 12 and 24 h following the discontinuation of the administration of the midazolam. Blood was kept at 4 °C and centrifuged within 24 h, the plasma being stored at -20 °C until analysed for total plasma midazolam concentration using gas–liquid chromatography (Howard, McClean and Dundee, 1985). The coefficient of variation of the method of analysis was 4% over the range of concentrations obtained in this study. As far as possible blood volume, arterial pressure, temperature and acid–base state were kept constant, and within their normal physiological ranges during the period of study.

Individual clearances from each patient in the infusion group were obtained using the formula:

$$\text{Clearance} = \frac{\text{infusion rate}}{\text{concentration at steady state}}$$

Terminal slopes in all patients were calculated by least squares regression using log concentration against time from 2 h after discontinuation of therapy. Half-lives were then calculated using the formula:

$$T_{\frac{1}{2}}^{\beta} = \frac{\log_e 2}{\text{terminal slope}}$$

RESULTS

One patient receiving midazolam by infusion showed an atypical response with high plasma concentrations, a long elimination half-life and a very low morphine requirement (8 mg in 16 h). This patient was excluded from all calculations and is discussed later.

Table I shows that the two groups of patients were broadly comparable with respect to age, gender, weight and duration of bypass.

The average duration of midazolam therapy was 16 h in both groups and the mean dose of midazolam was 34 mg in both groups. All patients were successfully weaned from mechanical ventilation in an average of 2.75 h in the infusion group and 2.5 h in the intermittent injection group, after the withdrawal of the midazolam. Blood loss (approximately 500 ml) and volume of blood products administered (approximately 1600 ml) during the period of midazolam therapy were similar in both groups.

The mean morphine requirements were 62 mg (range 38–93 mg) in the intermittent injection group and 52 mg (18–71 mg) in the infusion group. These did not differ significantly. Two patients having intermittent injections required morphine 93 mg during the period of therapy, whereas the maximum individual morphine requirement in the infusion group was 71 mg.

Figure 1 shows the decay in plasma concentrations following the initial midazolam 2.0 mg, the trough plasma concentrations in the intermittent injection group and the plasma concentrations obtained during the infusion. A steady plasma concentration was rapidly attained with the infusion and maintained during the period of study. Estimation of trough concentrations showed a delay of 6–8 h in attaining a steady state with intermittent injection.

The near-peak plasma concentrations (ng $\text{ml}^{-1} \pm$ SEM) averaged 92±9.5 at 4 h, 107±9.4 at 8 h and 102±12.7 at 12 h.

Figure 2 shows similar decays in mean plasma concentrations in both groups following the discontinuation of therapy. Concentrations decreased to very low values within 6 h, and by 24 h midazolam could not be detected in the plasma.

The clearance averaged 335±31.9 ml kg^{-1} h^{-1} in the infusion group. Individual elimination half-lives averaged 5.1 h (range 3.3–7.1) with

TABLE I. *Physical characteristics and time on bypass in both groups (mean ± SEM)*

Mode of administration	Age (yr)	Sex	Weight (kg)	Pump time (min)
Infusion (n = 9)	58±2.7	6M	70±3.9	85± 9.8
Intermittent (n = 10)	50±3.7	6F	65±3.0	78±10.0

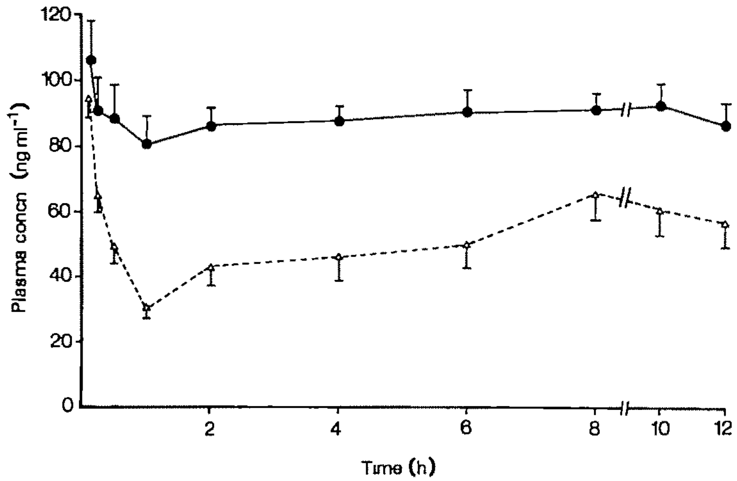

FIG. 1. Mean plasma concentrations (±SEM) over 12 h associated with the intermittent injections (trough) (△——△) or infusion (●——●) of midazolam.

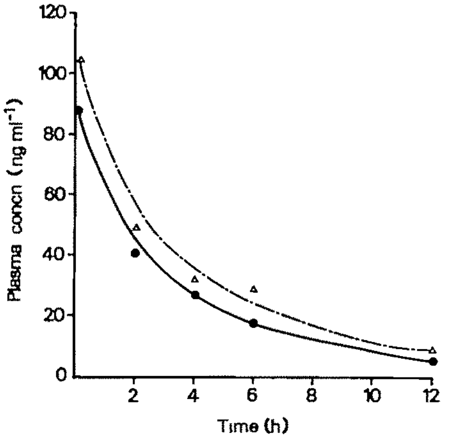

FIG. 2. Mean plasma concentrations (±SEM) following discontinuation of midazolam. △–·–△ = Intermittent injections; ●——● = infusion.

intermittent injection and 4.5 h (range 2.0–7.1) with infusions.

The patient previously mentioned with an abnormal elimination half-life was female, aged 55 yr and weighed 54 kg. Her urine output was satisfactory during the period of study and liver function was normal. This patient was weaned from mechanical ventilation 3 h after discontinuing the infusion, but remained very drowsy for the next 24 h. Figure 3 compares the plasma concentrations of midazolam obtained in this patient with the mean of the other nine patients receiving an infusion. In contrast to the findings in the other patients, midazolam was present in the 24-h sample and $T_{\frac{1}{2}}^{\beta}$ was 15.6 h in this patient. Clearance was 236 ml kg^{-1} h^{-1}.

DISCUSSION

The clearance and elimination half-lives found in this study are similar to previously reported values obtained following cardiopulmonary bypass (Harper et al., 1985). Despite the severe physiological upset of cardiopulmonary bypass, the elimination half-life of midazolam was only slightly longer than that obtained in association with other forms of surgery.

The concentrations of midazolam necessary for adequate sedation (80–100 ng ml^{-1}) were attained rapidly and remained relatively stable in patients receiving midazolam by infusion when compared with the 6–8 h delay associated with intermittent injection. With the latter, trough concentrations were very low during the first 4–6 h and there was a considerable difference between the peak and trough values indicating, possibly, a swing from adequate to light sedation. This agreed with the clinical impressions of the nursing and medical staff that sedation was better with the infusion—particuarly during the first few hours. The plasma concentrations on weaning from the ventilator were less than 40 ng ml^{-1}, the value considered necessary to achieve any sedative effect (Allonen, Ziegler and Klotz, 1981).

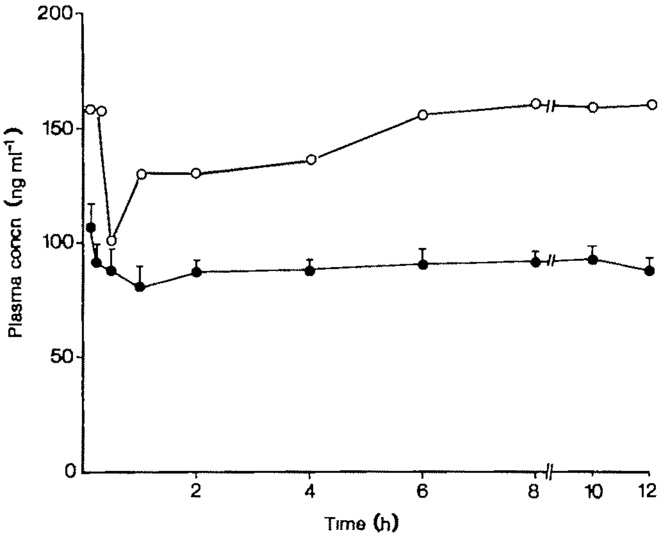

FIG. 3. Mean plasma concentrations (± SEM) (infusion) (●——●) compared with those obtained in a patient with an abnormal half-life for midazolam metabolism (○——○).

The one patient with a long elimination half-life would appear to be a slow metabolizer of the drug. Dundee and colleagues (1986) found this in about 6% of over 200 patients and a 1:20 occurrence in this study is a similar frequency.

Midazolam administered by a bolus dose of 2 mg followed immediately by an infusion at 2 mg h^{-1} is a safe and simple method of providing sedation during short-term ventilatory support after open-heart surgery. On account of its simplicity, this dosage regimen is preferred to more complicated regimens in which the drug is given on a weight basis, or in decreasing concentration. In patients who are normal metabolizers of the drug there is no risk of cumulation with this method of administration, and midazolam concentrations decrease rapidly following the discontinuation of the infusion. However, in about one patient in 20 there is a risk of a slow metabolism of the midazolam leading to cumulation with prolonged hypnotic effect after discontinuation.

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INFLUENCE OF SPINAL AND GENERAL ANAESTHESIA ON HAEMOSTASIS DURING TOTAL HIP ARTHROPLASTY

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SUMMARY

One hundred and one patients with osteoarthritis were randomly allocated to undergo total hip arthroplasty under either spinal (subarachnoid) or general anaesthesia. Venous blood was sampled before, during and after surgery and on the 5th day after operation to study the haemostatic mechanism. There were no preoperative differences between the two anaesthetic groups. Although there was pronounced individual variability, similar patterns of change in coagulation, platelets and fibrinolysis were seen in both groups. However, there were significant differences between the two groups in platelet count, thrombin production, and Factor VIIIRAg in the intra- and immediate postoperative periods. Also, compared with general anaesthesia, there was less intraoperative activation of fibrinolysis, as measured by the euglobulin clot lysis time, with spinal anaesthesia. These differences suggest slight modification of the haemostatic response to surgery with spinal anaesthesia, which could be consistent with a neuroendocrine mechanism. By the 5th day both groups exhibited a very similar "hypercoagulable" postoperative state.

Anaesthetic agents and techniques may influence the haemostatic response to surgery through a number of mechanisms: the membrane-stabilizing effects of local anaesthetics (Cooke et al., 1977); the direct cellular effects of volatile anaesthetic agents (Dalsgaard-Nielsen, 1979); the modification of the neuroendocrine response to surgery (Hall, 1985); changes in regional blood flow (Modig, Malmberg and Karlstrom, 1980), and changes in blood loss and transfusion requirements (Gray and Mackie, 1983). In total hip arthroplasty, recent reports suggest that the anaesthetic technique influences both the haemostatic response (Modig et al., 1983a) and the incidence of postoperative deep vein thrombosis (Thorburn, Loudon and Vallance, 1980; Modig et al., 1983b). This paper reports a randomized prospective study of the coagulation, platelet and fibrinolytic responses to total hip arthroplasty (THR), under either subarachnoid or general anaesthesia, undertaken to determine whether the perioperative haemostatic response to surgery was influenced by the anaesthetic technique used.

PATIENTS, MATERIALS AND METHODS

Patients

One hundred and one patients (55 women) with osteoarthritis of the hip gave written informed consent to the study, which was approved by the Hospital Ethical Committee. Patients without a history of thromboembolic disease and presenting with osteoarthritis of the hip joint were studied. Aspirin was stopped 1 week before surgery and other anti-inflammatory drugs on the day before operation. The sexes were separately randomized to receive either subarachnoid (SAB group), or general anaesthesia (GA group).

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Clinical and anaesthetic management

Diazepam 10 mg was given orally as premedication, 90 min before surgery. Before the induction of anaesthesia antiembolism stockings (TED, Kendall) were put on, electrocardiographic and arterial pressure monitoring commenced and an i.v. infusion established.

In the GA group, following fluid loading with acetated Ringer's solution, morphine 0.25 mg/kg body weight was given i.v., anaesthesia was induced with sodium thiopentone, and neuromuscular blockade was obtained with tubocurarine 0.5 mg kg^{-1}. The trachea was intubated, and anaesthesia maintained with nitrous oxide in oxygen (2:1 ratio) with normocapnic intermittent positive pressure ventilation. Halothane, up to 1%, and incremental doses of tubocurarine were given as indicated clinically. At the end of surgery, residual neuromuscular blockade was antagonized with neostigmine 2.5 mg (combined with atropine 1.2 mg).

For subarachnoid anaesthesia, fluid loading was commenced and the patient positioned lying on the non-surgical side with 10° head-down tilt. The subarachnoid space was identified using a routine sterile midline or paramedian approach at either the 3rd or 4th lumbar space. Anaesthesia was induced with a hypobaric solution of 1% amethocaine 10–15 mg, in sterile water. Light basal sedation was provided with morphine sulphate followed by 0.8% chlormethiazole (Heminevrin) infusion. These patients breathed oxygen-enriched air throughout surgery. In one man light general anaesthesia was required for skin closure towards the end of surgery. The aim of both anaesthetic techniques was to achieve modest hypotension for surgery.

An Exeter total hip arthroplasty was performed via the postero-lateral approach using a standard procedure without trochanteric osteotomy. Pressure injection of methylmethacrylate cement and a polyethylene femoral cement restrictor were used. During the operation, crystalloid and blood replacement followed a strict regimen based on surgical time, body weight, haematocrit and measured blood loss. Hypotension was managed with fluids and posturing alone. Vasoactive drugs were not used—either in the spinal anaesthetic solution or systemically—to manage hypotension, to avoid any possible interference with the haematological or metabolic studies.

Blood sampling

Five venous blood samples each from a fresh venepuncture site remote from the infusion site were taken:

(1) Sample A—before the induction of anaesthesia.
(2) Sample B—30 min after the start of surgery.
(3) Sample C—5 min after insertion of the femoral component.
(4) Sample D—30 min after the completion of surgery.
(5) Sample E—5 days after the operation.

Approximately 25 ml of blood was drawn without a tourniquet through a 20-gauge needle using three syringes: 4.5 ml of blood from syringe 1 was placed into an EDTA Venoject tube (tube 1); from syringe 2, 2.5 ml went into a β-thromboglobulin tube (RIA kit, Amersham) (tube 2) and 2 ml into a fibrin degradation products tube containing trasylol (tube 3). From syringe 3, 16.5 ml went into three separate tubes containing 3.13% trisodium citrate to give different dilutions (tube 4: 2.4 ml with 0.6 ml; tube 5: 9 ml with 1 ml; tube 6; 4.5 ml with 0.5 ml. All tubes were immediately placed in an ice-water bath for transport to the laboratory.

Samples were processed as follows: on arrival in the laboratory (5–10 min after venepuncture for intraoperative samples; maximum 30 min for sample E) platelet-poor plasma (PPP) was prepared from tubes 2, 4 and 6, which were centrifuged at 2550 *g* for 10 min at 4 °C. After separation, the fresh PPP was divided for immediate assay of prothrombin time, PTT, PTTK, thrombin time, thrombin generation index and fibrinogen, or for storage at −20 °C for subsequent batch processing of other tests. Platelet-rich plasma was prepared from tube 5 by centrifuging at 170 *g* for 10 min at room temperature, part removed and then the remaining plasma was centrifuged at 2550 *g* as described above and the PPP separated.

Haematological assays

The assays performed, their normal ranges for this laboratory and the source references for each method are shown in table I. The full blood count was performed on a Coulter S+2.

Statistical analysis

The biostatistics computer package BMDP (Dixon, 1981) was used for statistical analysis. The overall loss of data from sampling difficulties

TABLE I. *Haematological tests performed (normal ranges for this laboratory and the methodological source reference shown)*

Test	Normal range	Source reference
Haemoglobin	M: 130–180 g litre^{-1} F: 115–165 g litre^{-1}	Dacie and Lewis (1975)
Haematocrit	M: 0.40–0.54 F: 0.37–0.47	Dacie and Lewis (1975)
Platelet count	150–400 $\times 10^9$ litre^{-1}	Dacie and Lewis (1975)
Prothrombin time	0.8–1.2 ratio	Quick (1935)
Partial thromboplastin time (unactivated) (PTT)	0.8–1.2 ratio	Dacie and Lewis (1975)
Partial thromboplastin time (activated) (PTTK)	0.8–1.2 ratio	Matchett and Ingram (1965)
Thrombin time (TT)	30–40 s	Dacie and Lewis (1975)
Fibrinogen	2–4 g litre^{-1}	Ellis and Stransky (1961)
Fibrin degradation products (FDP)	Up to 10 mg litre^{-1}	Wellcome (1983)
Euglobulin clot lysis time (ECLT)	100–240 min	Biggs (1972)
Thrombin generation index (TGI)	14–44	Peck (1979)
Factor VIII coagulent activity (FVIIIC)	50–200 %	Casillas, Simonetti and Pavlosky (1971)
Factor VIII related antigen (FVIIIRAg)	50–200 %	Laurell (1966)
Anti Xa (chromogenic)	70–140 %	Odegard, Lie and Abildgaard (1976)
Antithrombin III biological (ATIII (bio))	75–135 %	Biggs (1972)
Antithrombin III immunological (ATIII (immuno))	68–140 %	Laurell (1966)
β-Thromboglobulin (BTG)	10–30 ng litre^{-1}	Radiochemical Centre (1977)
Platelet factor 3 assay (PF3)		
Availability	1.46–1.78 ratio	Saleem, Kreig and Cieslica (1975)
Total	1.86–2.22 ratio	

and laboratory problems was 2.5%. Missing values were not imputed, patients were excluded from only those analyses for which they had missing values on the relevant variable. The preoperative values for each variable in the two anaesthetic groups were compared using *t* tests with an overall comparison using Hotelling's T2. Covariate analyses were then carried out separately for the perioperative period (samples B, C and D) and the postoperative sample E, with the pre-induction value (sample A) as the covariate in both sets of analyses. Where sphericity assumptions were violated, individual comparisons were carried out using *t* tests. The Bonferroni correction for multiple comparisons was applied so that $\alpha = 0.0125$ or $\alpha = 0.007$, depending on the number of comparisons.

In the analysis of perioperative changes in platelets, Factor VIIIC, Factor VIIIRAg, Anti-Xa and Antithrombin III the effect on these specific component assays of acute haemodilution from i.v. infusion and intraoperative blood loss was corrected for by the ratio of the sample A haematocrit to that of the observed sample (B, C or D) for each patient as advocated by Richard and colleagues (1983). Finally, the results obtained on the 5th day were compared with the pre-induction values using *t* tests.

RESULTS

There were no statistically significant differences between the two groups before operation in either the clinical variables (table II) or the 19 haematological indices measured (table I). Mean intraoperative blood loss was 527 (SD 232) ml in the SAB group and 671 (SD 335) ml in the GA group ($t = 2.42$; $P < 0.02$). Intraoperative blood transfusion was required in 16 patients, four in the SAB group and 12 in the GA group (Chi-square = 5.81, $P < 0.025$), and in only one patient was this commenced before sample C had been taken. In the remaining 85 patients, if postoperative transfusion was required, this was not commenced until after sample D had been obtained. That consistent criteria for blood

TABLE II. *General data (mean (SD) as appropriate) for 101 patients undergoing total hip arthroplasty under spinal (SAB) or general (GA) anaesthesia.* * $P < 0.05$

	SAB ($n = 50$)	GA ($n = 51$)
Male:female	24:26	22:29
Age (yr)	66.7(8.8)	66.2(10.0)
Weight (kg)	70.6(14.8)	69.9(11.0)
Duration of surgery (min)	73.5(13)	78.6(22)
Blood loss (ml) (intraoperative)	527(232)	671(335)*
Patients transfused during operation	4	12*

transfusion were used in the two anaesthetic groups is demonstrated by the almost identical changes seen in mean haematocrit in samples A–D (table IV).

Routine coagulation screen

No abnormalities of haemostasis were detected on routine preoperative screening (table III). The PTT decreased slightly during operation (table III) (analysis of covariance: time, $P = 0.02$), but there were no differences between the two anaesthetic groups. PTTK did not change significantly during surgery, and there were no significant differences between the two groups. Both PTT and PTTK showed a significant reduction at sample E (PTT, $P = 0.0001$; PTTK, $P < 0.0001$) in both anaesthetic groups. Thirty-two patients showed an increase in postoperative FDP, 16 in each group.

Platelet count (table IV)

The haemodilution-corrected platelet count increased significantly during surgery in the GA group, but only slightly in the SAB group (covariate analysis: time, $P = 0.1$; anaesthesia, $P < 0.0001$; time–anaesthesia interaction, ns). By the 5th postoperative day the platelet count had increased markedly and to a similar extent in both groups (table IV).

Thrombin generation index (TGI) (fig. 1)

During the operation there was a significant difference in TGI between the two groups (covariate analysis: time, $P < 0.0001$; anaesthesia,

TABLE III. *Non-activated and activated partial thromboplastin times, prothrombin and thrombin times and fibrinogen in patients undergoing total hip arthroplasty under spinal (SAB) or general (GA) anaesthesia. Mean (1 SD). See text for samples times.* † $P = 0.02$; *** $P < 0.001$; **** $P = 0.0001$

	Sample A	Sample B	Sample C	Sample D	Sample E
PTTK ratio					
SAB	0.97(0.07)	0.99(0.10)	0.98(0.13)	0.97(0.10)	0.90(0.12)****
GA	0.95(0.13)	0.96(0.10)	0.94(0.09)	0.93(0.13)	0.87(0.11)****
PTT ratio					
SAB	1.00(0.15)	0.96(0.15)	0.97(0.16)	0.94(0.18)†	0.93(0.14)***
GA	0.99(0.13)	0.96(0.14)	0.95(0.14)	0.92(0.15)†	0.94(0.12)***
PT ratio	1.01(0.06)	—	—	—	—
TT (s)	34.4(3.5)	—	—	—	—
Fibrinogen (g litre^{-1})	4.1(1.4)	—	—	—	—

TABLE IV. *Platelet count and haematocrit (mean and 1 SD). SAB = Spinal anaesthesia; GA = general anaesthesia. Correction factor based on the change in haematocrit (Richard et al., 1983). See text for sample times.* **** $P = 0.0001$ *for difference from sample A*

	Sample A	Sample B	Sample C	Sample D	Sample E
Platelet count ($\times 10^9$ litre^{-1})					
Uncorrected					
SAB	277(75)	238(69)	236(68)	234(68)	326(82)****
GA	275(64)	267(67)	256(66)	261(72)	324(83)****
Corrected					
SAB	—	268(69)	279(80)	273(70)	—
GA	—	292(76)**	296(81)**	295(95)**	—
Haematocrit (%)					
SAB	42(4)	36(4)	34(4)	35(4)	—
GA	41(4)	37(4)	35(4)	36(4)	—

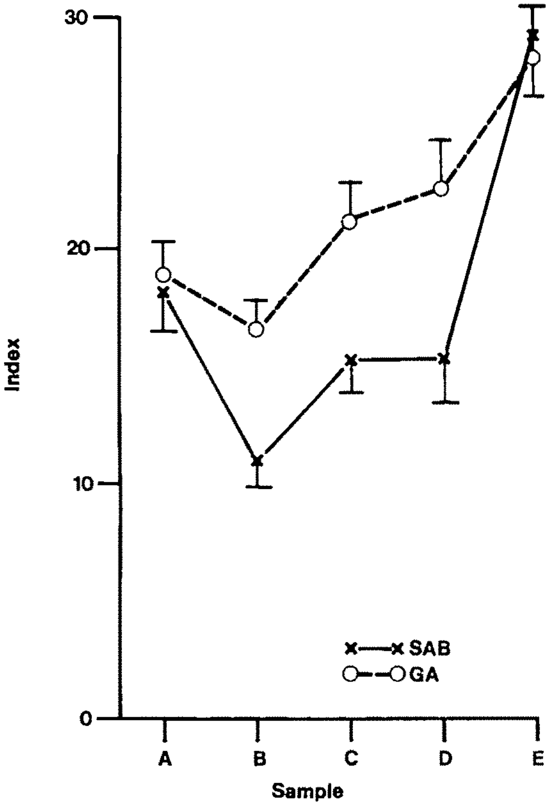

FIG. 1. Thrombin generation index (mean and SEM). SAB = Spinal anaesthesia; GA = general anaesthesia. See text for sample times and statistics.

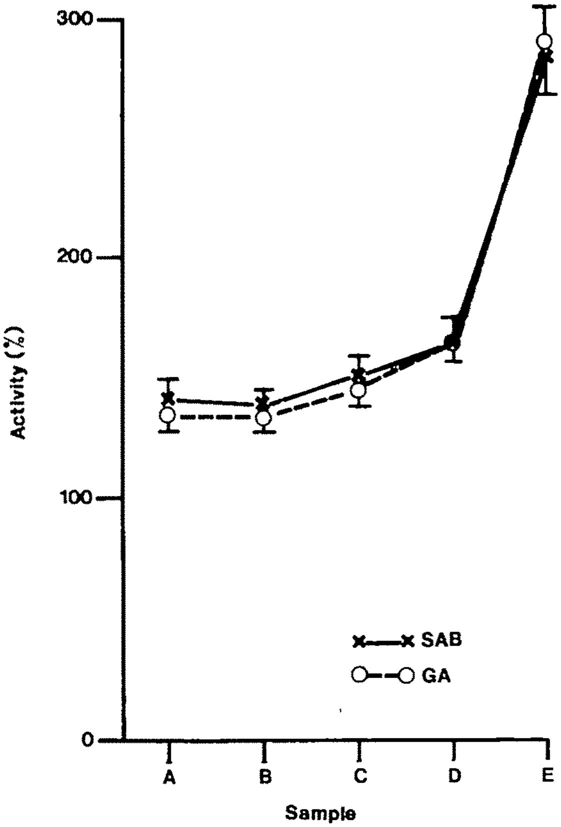

FIG. 2. Factor VIIIC (mean and SEM). SAB = Spinal anaesthesia; GA = general anaesthesia. See text for sample times and statistics.

$P < 0.0001$; time–anaesthesia interaction, ns). Comparing intraoperative with preoperative values, the SAB group showed a significant reduction in TGI at sample B ($P < 0.0001$), which returned toward the preoperative value for samples C and D. The GA group showed a slight but statistically insignificant increase in the perioperative period. By the 5th day following surgery TGI had increased markedly in both groups ($P = 0.0001$).

Factor VIIIC and Factor VIIIRAg (figs 2 and 3)

The haemodilution-corrected intraoperative values for FVIIIC showed little or no change, whilst in the early postoperative period (sample D) there was a small but significant increase compared with preoperative values in both groups (covariate analysis: time, $P < 0.0001$; anaesthesia, ns; time–anaesthesia interaction, ns). The corrected FVIIIRAg did not change during the perioperative period in the SAB group, but increased significantly in the GA group at sample D ($P = 0.0005$). The difference in pattern between the two groups was significant (covariate analysis: anaesthesia, $P = 0.04$; time, $P < 0.0001$; time–anaesthesia interaction, $P = 0.027$). By the 5th day there were similar large and significant increases in FVIIIC and FVIIIRAg in both groups.

Antithrombin III and Anti-Xa (chromogenic) (table V)

ATIII and Anti-Xa were measured in the first 57 patients only. The haemodilution-corrected values for ATIII (biological) demonstrated no intraoperative nor postoperative changes. For ATIII (immunological) a small decrease in corrected activity was seen during the operation in both groups (sample C, $P = 0.002$), returning toward normal by sample D. There were no differences between the two anaesthetic groups. The Anti-Xa chromogenic assay also decreased slightly during the operative procedure; this was

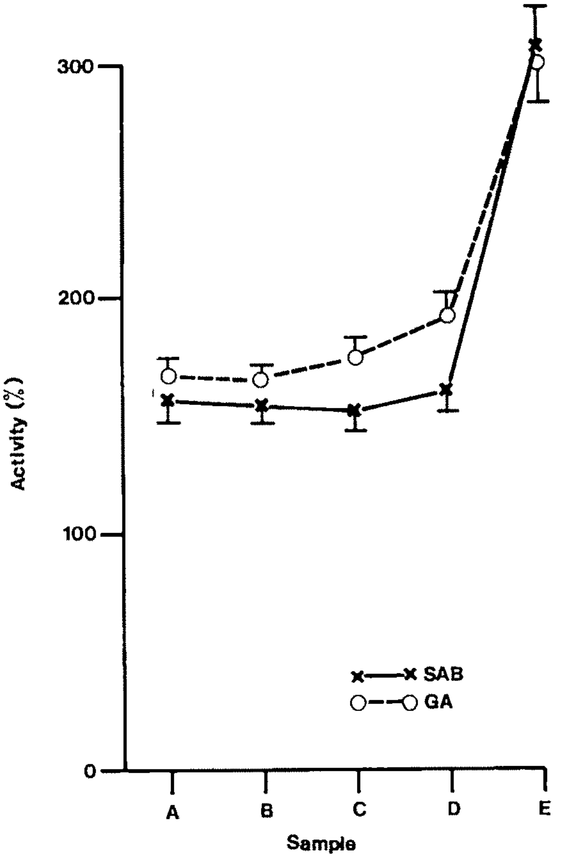

FIG. 3. Factor VIIIRAg (mean and SEM). SAB = Spinal anaesthesia; GA = general anaesthesia. See text for sample times and statistics.

more pronounced in the GA group (sample B, SAB group, ns; GA group, $P = 0.01$). However, there were no statistically significant differences between the two groups. ATIII and Anti-Xa activity was essentially normal on the 5th postoperative day.

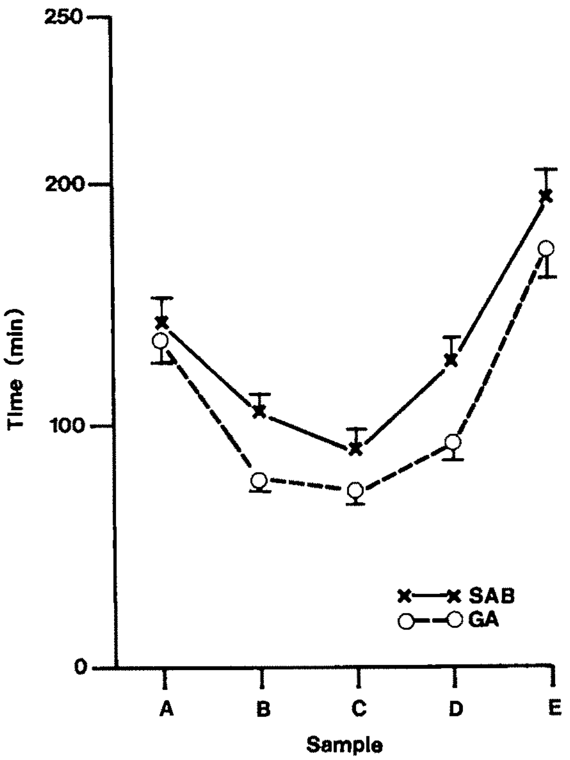

FIG. 4. Euglobulin clot lysis (mean and SEM). SAB = Spinal anaesthesia; GA = general anaesthesia. See text for sample times and statistics.

Platelet factor 3 (table VI)

Available PF3 and total PF3 were assayed in the first 57 patients. No specific changes were demonstrated either during or following operation in either group. There were no differences between the two anaesthetic groups.

Euglobulin clot lysis time (ECLT) (fig. 4)

Both groups exhibited a shortening of ECLT during surgery, followed by a prolongation after

TABLE V. *Antithrombin III (two methods) and anti-Xa (mean and 1 SD). SAB = Spinal anaesthesia; GA = general anaesthesia. Values shown corrected for haemodilution. See text for sample times and statistics*

	Sample A	Sample B	Sample C	Sample D	Sample E
ATIII (biological) (%)					
SAB	109(15)	108(17)	108(13)	105(13)	111(19)
GA	107(16)	103(17)	103(14)	100(14)	114(15)
ATIII (immunological) (%)					
SAB	106(21)	104(18)	100(14)	105(18)	110(16)
GA	108(20)	100(11)	98(17)	100(17)	112(27)
Anti-Xa (chromogenic) (%)					
SAB	160(27)	151(37)	152(43)	147(45)	155(37)
GA	157(22)	145(32)	146(51)	143(51)	173(60)

TABLE VI. *Platelet factor 3 (mean and 1 SD). SAB = Spinal anaesthesia; GA = general anaesthesia. See text for sample times and statistics*

	Sample A	Sample B	Sample C	Sample D	Sample E
PF3 (available) ratio					
SAB	1.7(0.3)	1.7(0.3)	1.8(0.3)	1.7(0.3)	1.6(0.3)
GA	1.6(0.3)	1.8(0.5)	1.7(0.3)	1.7(0.2)	1.6(0.2)
PF3 (total) ratio					
SAB	2.1(0.4)	2.2(0.4)	2.1(0.4)	2.0(0.4)	2.1(0.4)
GA	2.0(0.4)	2.1(0.4)	2.1(0.4)	2.1(0.4)	2.1(0.3)

surgery. There was a significant difference between the two anaesthetic groups in the degree of intraoperative fibrinolytic activation, this being less pronounced in the SAB group (covariate analysis: time, $P < 0.0001$; anaesthesia, $P = 0.003$; time–anaesthesia interaction, ns (fig. 4)).

β-Thromboglobulin (BTG)

The pre-induction values for BTG were increased markedly: SAB group 86(47) ng ml^{-1}; GA group 91(54) ng ml^{-1} compared with the normal range (table I). This increase did not correlate with age (correlation coefficient, $r = -0.05$) as previously reported (Zahavi et al., 1978). Considerable increases in BTG were seen in many patients during and following the operative procedure. However, in many samples the concentration exceeded the interpolation range for the assay (maximum 220 ng ml^{-1}) and, thus, these data were largely unusable.

DISCUSSION

Haemostatic response to surgical stress

On account of the considerable individual variability in measurements of haemostatic function under any conditions, it is essential for study groups to be of adequate size (Meade and North, 1977). This has often not been the case in studies during surgery, necessitating care in the interpretation of results, and probably accounting for some of the conflicting data in the literature.

Despite this, the intraoperative haemostatic reaction is now well documented (Ygge, 1970). During surgery enhanced fibrinolysis occurs, factors VIIIC and VIIIRAg concentrations decrease initially, and then increase (Britton et al., 1974; Butler et al., 1975; Griffiths, 1979) and evidence of platelet activation is seen (O'Brien et al., 1984). This is sometimes accompanied by a decrease in platelet count and reduced ATIII (Gaszynski, Lewicki and Pruszynska-Bednarek, 1976; Gitel et al., 1979). These latter changes, which parallel intraoperative changes in haematocrit occur even with minimal surgical trauma. This is probably a result of haemodilution, which should be corrected for before analysis (Laks et al., 1976; Fredin et al., 1983; Richard et al., 1983).

In the present study, changes very similar to these were seen, although there were some differences between the two anaesthetic groups in the perioperative period. These differences included an absence of the immediate postoperative increase in FVIIIRAg activity, minimal change in platelet count and less activation of fibrinolysis in the SAB group compared with the GA group. The perioperative reduction in thrombin generation index in the SAB group was significant, especially since some workers (von Kaulla and von Kaulla, 1964; Zuck and Bergin, 1973; Peck, 1979) consider this laborious test, which is a non-specific but sensitive measure of the coagulation system, to be valuable in the identification of the hypercoagulable state. The differences between the two anaesthetic groups in these variables, but not in PTT and PTTK, suggest only a minor modulation of the haemostatic response by spinal anaesthesia compared with general anaesthesia.

Our attempts to assay platelet function in the present study were disappointing. PF3 showed no changes during surgery, whilst BTG, a marker of the platelet release reaction (Zahavi and Kakkar, 1980), proved too sensitive in our hands, with many values exceeding the interpolative range. In addition, a longitudinal analysis of the BTG data suggested a major break in the pattern of results at about half way through the study. This could not be accounted for by either a change in blood sampling technique to which this assay is exquisitely sensitive, or laboratory error, although the high preoperative values suggest a methodological error must have been present.

Following major surgery, many patients develop an apparent "hypercoagulable state" manifested by prolonged euglobulin clot lysis time (Mansfield, 1972), increased platelet count and platelet coagulant activity (Walsh et al., 1976) and a marked increase in FVIII and fibrinogen (Hawkey et al., 1983). These changes have been reported to be similar following both laparotomy and THR. In the present study similar features were observed on the 5th postoperative day, irrespective of the anaesthetic technique used. At what stage the differences between the two anaesthetic groups in the immediate perioperative period disappear cannot be ascertained from the present data.

The direct effects of the anaesthetic agents and techniques used in this study on haemostasis are probably of minor importance compared with the response to surgery. Valium premedication suppresses the pre-induction activation of fibrinolysis seen in many patients, presumably through its anxiolytic effects (Mansfield, 1972), and such activation was not seen in the present study. Although, *in vitro*, halothane produces a dose-dependent inhibition of ADP-induced platelet aggregation (Ueda, 1971), results of *in vivo* studies have been conflicting (Korfel, Bielawiec and Mysliwiec, 1979; Lichtenfeld, Schiffer and Helrich, 1979; Gotta et al., 1980). Opioids appear to have no effect on platelet activity *in vivo* (Banasik, 1975; Gotta et al., 1980). However, acute respiratory alkalosis causes enhanced coagulation and fibrinolysis in the absence of surgical stress (Tanaka, 1970), and we were careful to avoid this in the GA group by monitoring end-tidal carbon dioxide concentration during mechanical ventilation and maintaining normocarbia (Richard et al., 1983).

Neuroendocrine response and haemostasis

Clinical stresses such as myocardial infarction induce a haemostatic response similar to that seen in association with surgery, suggesting a common reaction pattern to stress irrespective of its nature and of tissue damage (Chakrabarti, Hocking and Fearnley, 1969). Exercise and catecholamine infusion studies (Cash and Allen, 1967; Schernthaner et al., 1983; Mant, Kappagoda and Quinlan, 1984; Small et al., 1984), show an acute response typified by increased fibrinolysis, FVIIIC, FVIIIRAg and platelet counts, but a variable platelet aggregation response. Both fitness (Williams et al., 1980) and age (Yokoyama et al., 1984) appear to modify these responses. The elderley and those with a history of myocardial infarction show an exaggerated platelet aggregation response to adrenaline (Schernthaner et al., 1983; Yokoyama et al., 1984). Whilst the FVIII responses correlate closely with adrenaline concentration and are blocked by propranolol (Small et al., 1984), activation of fibrinolysis is largely independent of catecholamines (Cash and Allen, 1967).

In the present study, the differences between the two anaesthetic groups in platelet count, thrombin generation index, factor VIIIRAg and euglobulin clot lysis time are consistent with a modification of this haemostatic stress response in the SAB group. However, no difference between the two anaesthetic groups in FVIIIC was seen, but would have been expected if this modification did have a neurogenic basis. On the other hand we have reported, in the same patients, that suppression of the neuroendocrine response to surgery did indeed occur in the SAB group, but not in the GA group (Davis et al., 1987).

In patients undergoing laparotomy under extradural blockade, the activation of fibrinolysis was less pronounced in those whose cortisol response was impaired (Engqvist, Askgaard and Funding, 1976). In another small study of patients requiring abdominal hysterectomy (Rem et al., 1981) minimal changes in the haemostatic responses, and no differences between extradural and general anaesthesia were seen, even though blockade to T4 dermatome effectively obtunded the neuroendocrine response to surgery in the extradural group. Recently, Bredbacka and coworkers (1986) repeated this study. Both Factor VIIIC and Factor VIIIRAg increased less with extradural than with general anaesthesia. There were no other differences, activation of coagulation and fibrinolysis being similar in extent with both anaesthetics.

Others have observed significant enhancement of fibrinolytic activity during hysterectomy with various anaesthetic techniques (Simpson et al., 1982). In that study, extradural anaesthesia was associated with enhanced intraoperative fibrinolysis as opposed to less activation with spinal anaesthesia in the present study. However, afferent blockade in the study by Simpson and colleagues (1982) was insufficient to suppress the adrenocortical response to abdominal hysterectomy.

The role of adrenocortical or sympathetic nervous activity and their blockade with regional anaesthesia in the modification of the haemostatic response to surgery remains uncertain, but the present study suggests that in major lower limb surgery neuroendocrine influences may be important.

Methyl methacrylate cement, air embolism and haemostasis

It was anticipated that the insertion of the femoral component might be a potent stimulus to the haemostatic mechanism. There was no haematological evidence for this in the present study. Other studies have also reported only minor, or no, changes with the insertion of methylmethacrylate cement (Gaszynski, Lewicki and Pruszynska-Bednarek, 1976), or with venous air embolism (O'Brodovich et al., 1983). Precordial Doppler recordings in our patients (unpublished observations) demonstrated venous air or fat embolism in almost all patients during operation particularly at this time.

Fibrinolysis and anaesthetic technique

The euglobulin clot lysis time, which is sensitive to the level of circulating plasminogen activator, decreases during surgery and later increases. After the operation there are increases in 2-antiplasmin (Taberner, Poller and Burslem, 1979) and tissue plasminogen activator inhibitors (Kluft et al., 1984). Despite these apparent indications of diminished fibrinolysis during the postoperative period, there is evidence of increased plasmin activity (Lane et al., 1982; Douglas et al., 1985). In the light of these complex interactions it is difficult to know how to interpret the likely significance of perioperative changes in tests of fibrinolysis.

Modig and co-workers (1983a) reported that "fibrinolysis inhibition activity" was significantly less during THR under extradural anaesthesia to T4 than under general anaesthesia. This was associated with increased concentrations of plasminogen activator, both during and after the operation in the extradural group, and therefore more effective fibrinolysis. This contrasts with less fibrinolytic activation during operation in the SAB group in the present study. In Modig's study (1983a), the use of subcutaneous ephedrine, and adrenaline in the extradural solution as well as the effects of bupivacaine itself, none of which was a contributing factor in the SAB group in our study, could explain these differences.

Whilst Modig and colleagues (1983a) considered that blood loss and transfusion rather than suppression of the neuroendocrine response were the key factors, this is much less likely in the present study, in which intraoperative blood loss was considerably less and only a small proportion of patients received transfusion during operation. Nevertheless, there was a statistically significant difference in blood loss and transfusion needs between our two groups and this influence cannot, therefore, be excluded. Despite the apparent differences in fibrinolytic response, significant reductions were seen in the incidence of postoperative deep vein thrombosis associated with regional anaesthesia compared with general anaesthesia in both these studies (Modig et al., 1983b; Davis and colleagues, unpublished observations).

The present study suggests that regional anaesthesia slightly modifies the haemostatic acute phase reaction to THR. As well as these changes to the constituents of the blood, the other two important aetiological factors in deep vein thrombosis are venous stasis and vascular damage. Regional techniques appear to enhance lower limb blood flow in the immediate postoperative period (Modig, Malmberg and Karlstrom, 1980; Foate, Horton and Davis, 1985) compared with general anaesthesia, and we have seen (Davis and colleagues, unpublished observations) major differences in leg blood flow during total hip replacement. Modification of both these components of Virchow's triad in the immediate perioperative period, even if only to a minor degree, helps to explain the apparent beneficial effect of regional anaesthesia on the incidence of postoperative thromboembolic disease.

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DISPOSITION OF NALBUPHINE IN PATIENTS UNDERGOING GENERAL ANAESTHESIA

J. W. SEAR, M. KEEGAN AND B. KAY

SUMMARY

The pharmacokinetics of nalbuphine 20 mg i.v. were studied in 10 patients undergoing lower abdominal or body surface surgery. Blood sampling was carried out for 600 min after injection and drug concentrations were measured by HPLC using electrochemical detection. Disposition was best described as a triexponential function, with a mean elimination half-life of 135.5 min. Mean residence time, clearance, and volumes of distribution, V^{ss} and V^{β}, were determined by a model independent method, and gave mean values of 149.7 min (MRT), 1095 ml min^{-1} (Cl_p), 159.9 litre (V^{ss}) and 207.1 litre (V^{β}).

Nalbuphine is an agonist–antagonist opioid, structurally similar to oxymorphone. It is an effective analgesic with a potency comparable to that of morphine 8–10 mg (Beaver and Feise, 1978). Nalbuphine offers several potential advantages if used during balanced anaesthesia: haemodynamic stability, a ceiling effect on ventilatory depression at doses of about 0.5 mg kg^{-1}, rapid recovery of wakefulness, and a low incidence of nausea and vomiting after surgery. Its efficacy in suppressing reflex activity during laryngoscopy, tracheal intubation and intestinal traction is limited (Fahmy, Sunder and Roberts, 1982; Kay Healy and Bolder, 1985).

In the present study we present data on the plasma concentrations and disposition of nalbuphine when 20 mg was administered i.v. during anaesthesia for lower abdominal surgery.

PATIENTS AND METHODS

Ten patients (eight female; ages 24–61 yr, weights 53–81 kg, ASA I or II) were studied after giving informed consent. No patient had clinical evidence of renal, hepatic, cardiac or pulmonary disease. None had received, during the previous 7 days, drugs known to influence hepatic blood flow or hepatic microsomal enzyme activity.

Patients were premedicated with diazepam 10 mg 1.5–2 h before surgery. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1} and after neuromuscular transmission had been blocked, the trachea was intubated and the lungs ventilated with 67% nitrous oxide in oxygen at a rate of 12 b.p.m. and a tidal volume of 10 ml kg^{-1}. Halothane ($\leqslant 0.5\%$) or enflurane ($\leqslant 0.8\%$) was added to the inspired gas mixture.

Analgesia was provided by nalbuphine 20 mg i.v. Patients received Hartmann's solution 5 ml kg^{-1} h^{-1} to replace insensible and blood losses. During the operation, the ECG was recorded continuously, and arterial pressure measured at 5-min intervals by oscillotonometry. Analgesia after surgery was provided by papaveretum 10–15 mg i.m.

Nalbuphine 20 mg (Nubain), was diluted to 10 ml with sodium chloride 0.154 mol litre^{-1}, and given over 20 s via a peripheral infusion. Venous blood samples (6 ml) were collected via a separate cannula, placed in a vein in the contralateral arm, at 0, 1, 2, 5, 10, 15, 30, 45, 60, 90, 120, 180, 300 and 600 min after the administration of the drug. Heparinized plasma was separated by centrifugation, and stored at −20 °C until analysed in duplicate.

Drug analysis

Nalbuphine was measured by high pressure liquid chromatography using an electrochemical detector (Keegan and Kay, 1984) with naloxone

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hydrochloride as the internal standard. The sensitivity of the assay was 0.1 ng ml^{-1} and the coefficient of variation 1–3.5% at plasma concentrations between 10 and 100 ng ml^{-1}.

Data analysis

The decreases in plasma nalbuphine concentration after i.v. injection were analysed by non-weighted non-linear regression analysis (NONLIN) to determine the terminal half-life. However, initial estimates showed that the rapid distribution half-life of the triexponential model was less than 30 s for most patients and, because of the chosen sampling regimen, subject to considerable error. Consequently, further kinetic analyses were carried out using a non-compartmental approach, as described by Benet and Galeazzi (1979).

The general notation used in this paper is that defined by Hull (1979).

Data are presented as mean (±SD) except where otherwise indicated. The relationship between the age or the weight of the patient and the derived kinetic variables was investigated by linear correlation analysis.

RESULTS

Anaesthesia was uneventful in nine of the 10 patients; the remaining patient, a 41-year-old female, developed a sinus bradycardia (38 beat min^{-1}) and associated hypotension following the administration of the nalbuphine. These effects were readily corrected with atropine 0.3 mg i.v.

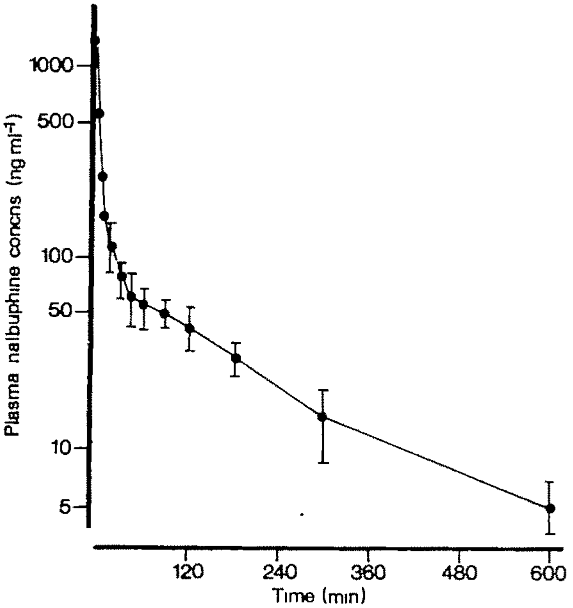

FIG. 1. Plasma nalbuphine concentrations (mean ± SD) following administration of 20 mg i.v. to 10 anaesthetized patients. For clarity, the SD bars have been omitted from the mean points at 1, 2, 5 and 10 min after injection.

The mean nalbuphine plasma concentration–time curve is shown in figure 1. The mean elimination half-life was 135.5 min. The derived kinetic parameters (clearance, volume of distribution at steady state (V^{ss}), apparent volume of distribution during the elimination phase (V^{β}) and mean residence time) are shown in table I.

Correlation analysis showed no relationship between body weight or age and systemic drug clearance and V^{ss}. The initial volume of distribution (V_1) varied between 0.73 and 13.55 litre (mean 5.84 litre).

TABLE I. *Derived pharmacokinetic parameters (mean ± SD) following i.v. injection of nalbuphine 20 mg in anaesthetized patients. Notation according to Hull (1979). MRT = Mean residence time*

Patient	$T_{\frac{1}{2}}^{\beta}$ (min)	MRT (min)	V^{ss} (litre)	V^{β} (litre)	Cl_P (ml min^{-1})	V^{ss}/V^{β}
1	131.0	140.8	191.97	257.81	1363.4	0.745
2	77.0	88.5	66.73	83.31	751.1	0.801
3	262.7	186.3	171.04	348.01	918.2	0.491
4	122.5	168.4	182.45	191.46	1083.3	0.953
5	173.8	196.9	187.85	239.26	954.2	0.785
6	115.6	150.4	154.94	171.77	1030.2	0.902
7	159.4	190.1	202.40	244.83	1064.5	0.827
8	139.7	165.0	167.51	205.48	1015.3	0.815
9	103.6	128.4	130.89	152.45	1019.5	0.859
10	69.8	81.9	143.37	176.26	1750.7	0.813
Mean	135.5	149.7	159.92	207.06	1095.0	0.799
SD	55.4	40.4	39.62	71.21	276.6	0.123

Plasma drug concentrations at extubation of the trachea varied between 30 and 62 ng ml^{-1}. In no patient was extubation delayed because of ventilatory depression.

DISCUSSION

Previously available data on the i.v. kinetics of nalbuphine relate to volunteer studies (Dupont: on file) and patients undergoing cardiac surgery (Lake et al., 1982). In the former studies, the quoted clearance values varied between 1.54 and 2.53 litre min^{-1}, and the elimination half-lives between 2.16 and 3.35 h. The results determined in the patients undergoing cardiac surgery indicated an elimination half-life of 3–3.5 h. The terminal half-life in patients in the present study (mean 136 min) was shorter than that reported for other synthetic opioids such as fentanyl (McClain and Hug, 1980), and buprenorphine (Bullingham et al., 1980). Recent work by Reilly and colleagues (1985, 1986) has suggested that the use of halothane or enflurane as a supplement to nitrous oxide in oxygen anaesthesia is accompanied by a decrease in liver blood flow and the intrinsic hepatic clearance of flow-dependent, high hepatic extraction ratio drugs such as propranolol. A similar alteration in the disposition of verapamil (decreased clearance and decreased volume of distribution) has been described during volatile-supplemented anaesthesia in the dog (Merin et al., 1985). By extrapolation, it is possible that a similar alteration in disposition has been seen with nalbuphine in the anaesthetized patient, as our patients show a lower clearance and reduced volume of distribution when compared with the results obtained in awake volunteers.

The kinetics in this study were based on plasma total drug concentrations. Data from healthy volunteers indicate that nalbuphine binds to plasma proteins to the extent of 25–40% over the concentrations range 1–100 ng mg^{-1}. Hence binding, and therefore disposition, are unlikely to be significantly affected by other drugs or volatile agents given concurrently during anaesthesia, or in the immediate postoperative period (Dale and Nilsen, 1984).

The volumes of distribution of nalbuphine (V^{β} and V^{ss}) are similar to those found for morphine (Murphy and Hug, 1981; Stanski, Greenblatt and Lowenstein, 1978) in the anaesthetized patient, but are less than those for the highly lipophilic opioid, methadone (Gourlay, Wilson and Glynn, 1982).

As a result of the sampling regimen adopted in this study, any estimates for π and α half-lives would be liable to considerable error. Hence, the kinetic parameters were determined by a non-compartmental approach involving determination of the area under the concentration–time curve, and its first statistical moment. The estimates for V_1 (0.73–13.55 litre) showed a 20-fold variability. This is further evidence of poor characterization of the hybrid constants describing the distribution phases, and probable overestimation of V_1 in some patients (Chiou, 1980).

Criticism may be levelled at the use of samples of venous blood. Major and coworkers (1983) have shown considerable differences in propofol concentrations in arterial, peripheral venous and central venous samples for up to about 60 s after the end of administration. Thereafter, no significant differences were observed. Thus, although drug disposition in body tissues is dependent on *arterial* drug concentrations, the overestimation of V^{ss}, when based on venous sampling, will be significant only if extensive tissue drug uptake occurs (Chiou, 1982). However, Chiou (1982) has suggested that the determination of V^{ss} by a physiological or model independent method will limit the magnitude of this overestimation. The value of V^{ss}/V^{β} was high in our patients (mean 0.773), indicating that the return of drug from peripheral tissues to the plasma will not be the rate limiting factor in drug clearance.

In summary, nalbuphine has a high systemic clearance, and will have an estimated hepatic extraction ratio of 0.5–0.7. On account of this high clearance, and the accompanying short elimination half-life (136 min), it should be possible to administer nalbuphine by continuous i.v. infusion and achieve constant blood concentrations during the operative period.

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COMPARISON OF NALBUPHINE, PETHIDINE AND PLACEBO AS PREMEDICATION FOR MINOR GYNAECOLOGICAL SURGERY

W. N. CHESTNUTT, R. S. J. CLARKE AND J. W. DUNDEE

SUMMARY

In a randomized double-blind placebo-controlled trial involving 80 patients nalbuphine 10 mg and 20 mg were compared with pethidine 100 mg and a placebo given i.m. at least 90 min before minor gynaecological surgery. Nalbuphine proved a suitable alternative to pethidine, producing beneficial sedation which was maximum at 60 min after injection. Both nalbuphine and pethidine reduced the excitatory sequelae of methohexitone induction. Increasing the dose of nalbuphine from 10 mg to 20 mg produced no significant additional sedation or intraoperative benefit. Short-lived pain at the injection site was a feature of the use of nalbuphine in either dose. The main disadvantage of nalbuphine was nausea and vomiting of delayed onset, the frequency of which was similar after either dose.

Nalbuphine is a semi-synthetic agonist–antagonist opioid providing analgesia broadly comparable to that associated with the administration of morphine, when used for the relief of moderate to severe pain (Beaver and Feise, 1978; Bahar, Rosen and Vickers, 1985). Miller (1980) suggested that nalbuphine had fewer disadvantages than any other parenterally administered strong analgesic. Nalbuphine exhibits a ceiling to its ventilatory depressant effects (Romagnoli and Keats, 1980) and can reverse ventilatory depression caused by other opioids (Moldenhauer et al., 1985). Psychotomimetic reactions are only seen at very high doses and it has low dependence liability (Jasinski and Mansky, 1972). The most frequent side effect is sedation, with gastrointestinal upset apparent in a few patients, although comparison between studies is difficult (Errick and Heel, 1983).

PATIENTS AND METHODS

Regional ethics committee approval was obtained. Eighty healthy women scheduled for minor gynaecological procedures and who had given verbal consent to participation in the study were randomly allocated to receive nalbuphine 10 mg, nalbuphine 20 mg, pethidine 100 mg or saline 2 ml at least 90 min before surgery. After i.m. injection of the contents of a coded ampoule by a nurse, each patient was visited at 20, 40, 60 and 90 min by one of the authors (W.N.C.), who was unaware of the drug given. Any beneficial or toxic effects were noted, as described by Dundee, Moore and Nicholl (1962).

Drowsiness was graded on an arbitrary basis into "marked (asleep)", "fair", "slight" or "absent". The presence or absence of pain at the injection site was noted, as was the occurrence of dizziness. Emetic sequelae were graded as "vomiting", "marked nausea", "slight nausea" or "nil".

A standard anaesthetic technique was used: methohexitone 1.6 mg kg^{-1} for induction followed by 70% nitrous oxide in oxygen with supplementary doses of methohexitone as required. The anaesthetists were unaware of the premedicant and the course of anaesthesia was observed as being "smooth" or "complicated", recovery being assessed, 2 min after the withdrawal of nitrous oxide, as "awake", "safe" or "unsafe". Patients were seen 1 and 6 h after surgery, when emetic or other sequelae were noted.

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TABLE I. *Characteristics of the four groups of patients (mean ± SEM)*

	Nalbuphine 10 mg	Nalbuphine 20 mg	Pethidine 100 mg	Saline 2 ml
Age (yr)	35±2.6	32±2.2	29±1.9	35±2.5
Weight (kg)	57±1.7	60±1.0	60±1.9	57±1.9
Premedication–induction interval (min)	150±8.7	140±9.4	136±7.7	168±10.5
Anaesthetic duration (min)	12.0±0.8	14.4±2.0	11.3±0.6	10.7±0.8
Total methohexitone dose (mg)	143±9.4	151±10.9	162±7.6	165±12.0

TABLE II. *Significant test results (Mann–Whitney U test) on the distribution of drowsiness in the preoperative period for the four groups: nalbuphine 20 mg (N_{20}), nalbuphine 10 mg (N_{10}), pethidine 100 mg (P_{100}) and saline 2 ml (S)*

	20 min	40 min	60 min	90 min
N_{20} v. N_{10}	ns	ns	ns	ns
N_{20} v. P_{100}	$P < 0.01$	$P < 0.05$	$P < 0.05$	$P < 0.05$
N_{20} v. S	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
N_{10} v. P_{100}	ns	ns	ns	ns
N_{10} v. S	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
P_{100} v. S	$P < 0.01$	$P < 0.001$	$P < 0.01$	$P < 0.05$

RESULTS

The groups were comparable with respect to age, weight, premedication–induction interval, duration of anaesthesia and duration of operation (table I). The average premedication–induction intervals were between 140 and 168 min because of the timing of the operating lists, but this did not affect the assessment of the drugs. Drowsiness was a significant feature of premedication with nalbuphine, the peak incidence being at 1 h after injection. Figure 1 shows the frequency of "notable" drowsiness (marked and fair) which was experienced at some time by all patients receiving nalbuphine 20 mg, by 16 of 20 given nalbuphine 10 mg, by 11 of 20 given pethidine 100 mg and by three of 20 given placebo. Drowsiness was significantly more frequent at all times when active premedication had been given (table II). Nalbuphine 20 mg was not significantly more soporific than nalbuphine 10 mg at any time, but both were consistently more so than pethidine.

Pain at the site of injection was noted frequently at 20 min. At this time 11 of 20 and 12 of 20 of those given nalbuphine 10 and 20 mg, respectively, reported pain, compared with only three of 20 after pethidine or saline. Nalbuphine injection caused more ($P < 0.05$) post-injection pain than the other preparations.

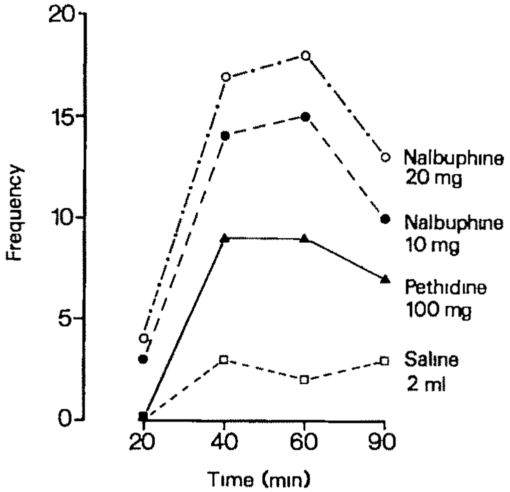

FIG. 1. Frequency of "notable" drowsiness (marked and fair) at four times after the premedicant regimens.

Pethidine produced dizziness in significantly more patients than the placebo ($P < 0.002$), 11 out of 20 experiencing this symptom at some time. Only five out of 20 and six out of 20 complained of dizziness after nalbuphine 10 mg and 20 mg, respectively, with one of 20 in the placebo group reporting this effect.

Nalbuphine, in either dosage, caused minimal

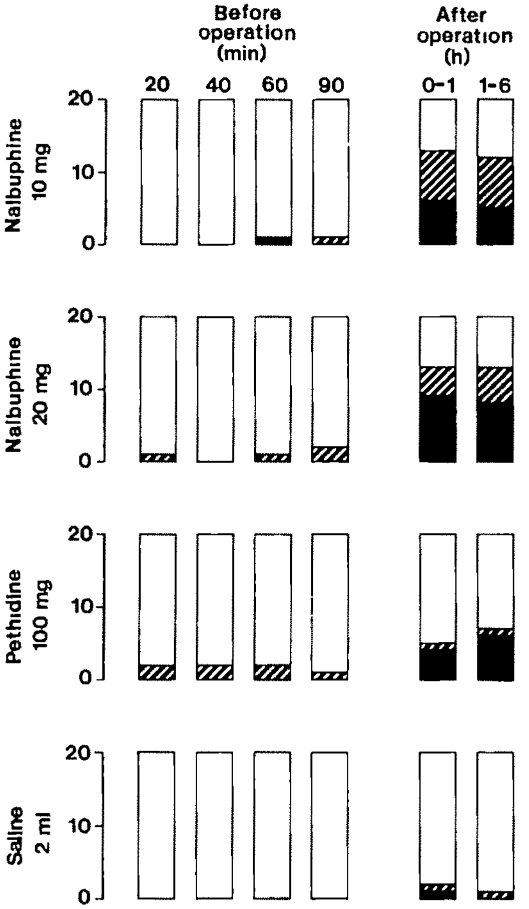

FIG. 2. Frequency of nausea (hatched areas) or vomiting (black areas) 20, 40, 60 and 90 min after the premedication, and 0–1 and 1–6 h after the end of anaesthesia.

preoperative emetic sequelae, the frequency of which did not differ significantly from those after placebo. In the postoperative period both doses caused significantly more ($P < 0.001$) gastrointestinal upset than the placebo, with 75–80% of subjects experiencing either nausea or vomiting at some time (fig. 2). There was no significant difference between the effects of the two doses. Pethidine 100 mg exhibited a significant emetic tendency compared with saline both before and after surgery ($P < 0.05$), but the incidence did not differ significantly from that with either dose of nalbuphine at any time. Psychotomimetic reactions were not seen in any patient.

Anaesthesia was consistently less disturbed ($P < 0.01$) after the active premedicant drugs. After nalbuphine 10 mg, 16 out of 20 had trouble-free anaesthesia compared with 13 out of 20 after either nalbuphine 20 mg or pethidine 100 mg. In contrast, in only five out of 20 was anaesthesia considered smooth following the placebo.

Recovery was comparable in all groups, from seven to 12 patients being awake in any group 2 min after the withdrawal of nitrous oxide.

DISCUSSION

Since the usual recommended analgesic dose is 10–20 mg for a 70-kg individual (Romagnoli and Keats, 1984; Pinnock, Bell and Smith, 1985), it seemed appropriate to study these two doses, in order to define the optimal dose for premedication, and to compare them with a standard dose of pethidine. Nalbuphine, as assessed by two different methods, appears to have an analgesic potency approximately 0.7 that of morphine (Beaver and Feise, 1978; Bahar, Rosen and Vickers, 1985). On the basis of the latter study, pethidine 100 mg is equivalent to nalbuphine 12.3 mg. Rita, Seleny and Goodarzi (1980) mentioned preliminary dose finding studies in children, then opted for a 0.2-mg kg^{-1} dose. Since the regimen used here resulted in doses of 0.17 mg kg^{-1} and 0.33 mg kg^{-1}, respectively, it clearly included a greater dose than previous work.

The present study confirms the previously reported sedative effect of nalbuphine which is thought to be an effect mediated via the kappa-receptor (Jasinski, 1984). After 20 mg all subjects exhibited drowsiness at some time. The 20-mg dose of nalbuphine did not produce significantly greater drowsiness than the 10-mg dose—a finding compatible with a flattening of the dose–response curve at the greater dose used in this study. However, this cannot be proved because of the qualitative nature of the assessments. Kay (1985), on the other hand, reported that the kappa-mediated sedative effect was still increasing as dosage was increased beyond that which caused maximal mu-receptor mediated ventilatory depression and analgesia.

Despite having an analgesic effect comparable to that of pethidine 80 mg, nalbuphine 10 mg was generally (but not significantly) more sedative than pethidine 100 mg. The time of maximal drowsiness was 1 h after injection and this may explain why Rita, Seleny and Goodarzi (1980) failed to show significant "calming" in children at the time of the induction, some 25–55 min after injection, yet did find significant "calming" subsequently—in the recovery room.

As expected, the induction of anaesthesia using methohexitone was significantly less troublesome following nalbuphine premedication at either dose than after placebo and did not differ from that after pethidine 100 mg. This is in agreement with the findings of Rita, Seleny and Goodarzi (1980), who found gaseous induction smoother after nalbuphine than after placebo and comparable to that associated with pentazocine premedication. Likewise, induction using thiopentone was trouble-free in the study of Pinnock, Bell and Smith (1985), who compared nalbuphine 10 mg with morphine 10 mg when given as premedication i.m. 1 h before anaesthesia for cervical dilatation and uterine curettage. This, however, is not a good test as, even without premedication, induction using thiopentone is usually smooth. In a placebo-controlled trial, nalbuphine was compared with morphine 0.1 mg kg^{-1} i.v. given some 12–16 min before the induction of anaesthesia for cervical dilatation and uterine curettage (Fragen and Caldwell, 1977). While not commenting on the smoothness of induction, they noted the total dose of thiopentone required to supplement the nitrous oxide–oxygen anaesthesia. Both opioids reduced the thiopentone dose by 13%, an insignificant amount. Our findings, therefore, are in agreement with previous work, indicating that nalbuphine does tend to smooth the process of induction, but does not significantly alter the dose of i.v. supplement required. Likewise, we found no difference in the recovery characteristics of the groups, a finding in agreement with that of Fragen and Caldwell (1977).

The first unpleasant sequel to the use of nalbuphine use was the unexpected, but significant, incidence of pain on injection. This was usually neither very prolonged, nor distressing: the discomfort had resolved by the 60-min visit in all but three of the 23 patients who experienced it. In a previous communication (Chestnutt, Clarke and Dundee, 1985) it was reported that pain at the injection site was consistently experienced by student volunteers in a single-blind crossover study, when nalbuphine 10 mg or 20 mg or saline was given by i.m. injection. Magruder, Christofforetti and DiFazio (1980) noted transient burning at the injection site in almost one-half the patients receiving an i.v. injection—a proportion similar to that found in this study. In contrast, Fragen and Caldwell (1977) noted pain at the site of an i.v. injection in only seven of 26 patients given nalbuphine, compared with four of 25 given morphine and five of 24 given pethidine.

The main disadvantage following the use of nalbuphine was the delayed onset of nausea and vomiting, which was noted mainly in the postoperative period. This time pattern is similar to that following morphine (Dundee et al., 1975) and it was also found in the study of Pinnock, Bell and Smith (1985), who studied a population similar to that in the present study. The study on student volunteers (Chestnutt, Clarke and Dundee, 1985) showed that this nausea and vomiting was a delayed effect and could be experienced without undergoing anaesthesia. One subject in that crossover trial refused the second dose because of this effect. It was notable that increasing the dose from 10 mg to 20 mg produced little increase in emetic tendency or the incidence of dizziness. Pinnock, Bell and Smith (1985) found nalbuphine 10 mg to be comparable to morphine 10 mg as far as emetic sequelae were concerned. In clinical practice one would probably combine an opioid with an antiemetic such as atropine or hyoscine. As is the case with pethidine (Dundee, Moore and Clarke, 1964) and morphine (Clarke, Dundee and Love, 1965), these would probably decrease the emetic effects of nalbuphine, and such combinations would seem worthy of further study.

In conclusion, nalbuphine has been shown to be a suitable agent for premedication for minor surgery, particularly because of its sedative effect and its ability to smooth the course of anaesthesia in a spontaneously breathing patient. These benefits are offset by pain on injection, and a tendency to nausea and vomiting – which were particularly evident in the postoperative period.

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RECOVERY OF BOWEL MOTILITY AFTER SURGERY

Detection of Time of First Flatus From Carbon Dioxide Concentration and Patient Estimate after Nalbuphine and Placebo

H. YUKIOKA, D. G. BOGOD AND M. ROSEN

SUMMARY

Co-ordinated bowel motility has been studied after surgery. The time to first flatus (TFF) was noted by 20 patients aged 60 yr or older and measured simultaneously using a carbon dioxide analyser. After cystoscopy under general anaesthesia, 10 patients received nalbuphine 20 mg i.v., and 10 patients had placebo (normal saline). In 16 patients (80%) the two observed times coincided and there were no false reports. Two patients were asleep, and did not report TFF. In two others the sampling tube became obstructed. Therefore, both methods are of value; the carbon dioxide analyser, however, is a sensitive and accurate monitor of the initial passage of flatus which does not require patient co-operation. In the i.v. nalbuphine group, the median TFF was more than three times as long (212 min) as that in the placebo group (64 min) ($P < 0.01$).

An indication of the return of co-ordinated bowel motility following surgery is the passage of flatus. Previously, we have used this event to test the influence of drugs, especially opioids, on the re-establishment of bowel activity (Shah, Rosen and Vickers, 1984). However, there remains doubt as to how well the patient can note accurately the time at which flatus is first passed, especially if still recovering from the effects of sedative drugs. As flatus contains carbon dioxide (5–80% (Calloway, 1968)), we have compared the time to first flatus as noted by the patient, and as recorded by a carbon dioxide analyser.

PATIENTS, MATERIALS AND METHODS

Materials: Test of sensitivity

A Datex Normocap infra-red carbon dioxide analyser was linked to a Chessel 304 chart recorder. The sampling tip of the analyser was fixed 2 cm from a rubber membrane pierced by a hole through which various oxygen–carbon dioxide mixtures were injected with a gas-tight syringe. The minimum volume of gas required to produce a deflection equivalent to 0.5% carbon dioxide was noted, this concentration being arbitrarily selected as measurable easily and reproducibly.

A volume of 1 ml of gas gave a positive result, even at the lowest concentration of carbon dioxide (5%) in flatus (Calloway, 1968). The volumes of different carbon dioxide–oxygen mixtures needed to produce a deflection equivalent to 0.5% carbon dioxide are shown in figure 1.

Patients

Ethical approval for the trial was granted by the District Ethical Committee. All patients gave informed consent, and agreed to the administration of either a single dose of nalbuphine or placebo after surgery. Patients were free to withdraw from the trial at any time, and alternative oral analgesia was available.

Patients in ASA groups I and II, older than 60 years of age, undergoing minor procedures under general anaesthesia, were studied. Only moderate discomfort after surgery was expected.

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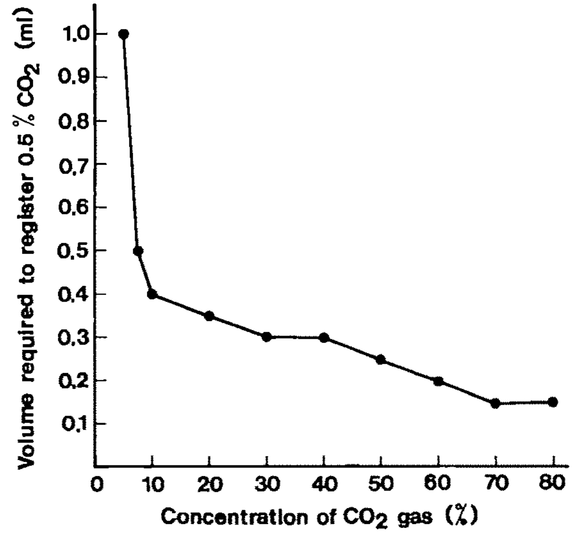

FIG. 1. Sensitivity of the apparatus to gas samples containing different concentrations of carbon dioxide. The volume indicated is that required to give a deflection equivalent to 0.5% carbon dioxide when the tip of the sampling tube is 2 cm from the syringe.

No patient had taken any analgesic drug in the 24 h before admission to the study.

Following an evening meal, patients fasted from midnight. Their procedures were scheduled for the following morning. No premedication was given. Anaesthesia was induced with thiopentone 3–4 mg kg^{-1} and maintained with either halothane or enflurane and nitrous oxide in oxygen. No opioids, neuromuscular blocking agents or vagolytics were administered.

Immediately on the patient's return to the ward, the carbon dioxide analyser was attached to the patient by a 200-cm fine plastic tube (outer diameter 2 mm), taped no more than 2 cm from the anus. Each patient then received (double-blind) either nalbuphine 20 mg or 0.9% sodium chloride in 2 ml i.v. according to a pre-randomized list. The patient was asked to note the time at which he was first aware of the passage of flatus. Each patient was observed continuously for 15 min and then visited hourly until he and the carbon dioxide analyser had recorded an episode of flatus.

Duration of anaesthesia, time from anaesthesia to the administration of the test drug (recovery time) and time from drug administration to passage of first flatus (TFF) were recorded by both methods. The incidence of drowsiness, nausea, vomiting and other side effects was noted. Results were analysed by the Mann–Whitney *U* test for non-parametric data.

RESULTS

Ten patients in each group underwent cystoscopy. All 10 patients in the placebo group were male, and in the nalbuphine group eight were male and two were female. The two groups are similar with respect to age and weight (table I).

The duration of anaesthesia and the recovery time were similar (table II). The TFF in table II is that recorded by the carbon dioxide analyser, except in two patients, both in the placebo group, in whom the sampling tube became obstructed, and the patients' estimates were used. Two other patients in the placebo group were excluded when they asked to withdraw from the trial at 110 and 210 min, respectively (before passing flatus), as they wished to get out of bed. These were replaced by two further patients. The median TFF in the nalbuphine group was 212 min, compared with 64 min in the control group ($P < 0.01$). (If the two patients had not been excluded, and their TFF

TABLE I. *Sex distribution and mean (SD) age and weight of patients*

	Age (yr)	Weight (kg)	Sex	
			M	F
Nalbuphine	70.7 (6.2)	72.8 (12.7)	8	2
Placebo	70.0 (5.9)	77.4 (16.5)	10	0

TABLE II. *Mean (SD) of anaesthetic time and recovery time and median (inter-quartile range) of TFF. *Significant difference* (P < 0.01)

	Duration of anaesthesia (min)	Time from anaesthesia to drug administration (min)	Time from drug administration to first flatus (min)
Nalbuphine	17.8 (7.9)	53.5 (12.9)	212.0 (152.5)*
Placebo	13.9 (4.2)	51.9 (8.0)	64.0 (102.5)*

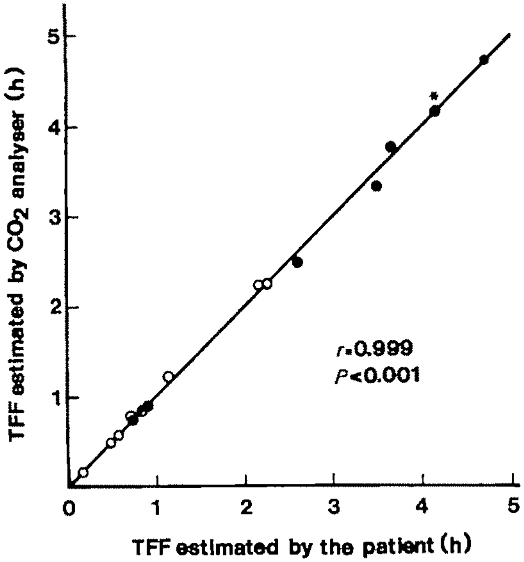

FIG. 2. Correlation between time to first flatus (TFF) as estimated by the patient and the carbon dioxide analyser. ○ = Patients in the control group; ● = patients in the nalbuphine group. The asterisk represents two patients with the same results.

recorded as the time at which they withdrew from the trial, the adjusted median (inter-quartile range) TFF in the control group would have been 95 (110) min—the difference still being significant at the 1% level.)

In 16 patients (80%) TFF was recorded both by the patient and the carbon dioxide analyser (fig. 2). A very close correlation was seen between the time to first flatus as estimated by both methods ($r = 0.999$; $P < 0.001$).

Patients who received nalbuphine experienced some drowsiness immediately after the injection. Two were asleep when flatus was recorded. Three patients complained of slight nausea after nalbuphine.

DISCUSSION

The passage of flatus is widely regarded as a good clinical indication of the return of co-ordinated bowel motility following surgery, and is probably more reliable than the onset of bowel sounds—which do not necessarily indicate a recovery of true propulsive peristaltic activity. In a previous trial Shah, Rosen and Vickers (1984) used this indicator to investigate the effects of premedication with morphine, nalbuphine and diazepam upon recovery of bowel function following minor surgery. That study showed a prolonged TFF in all groups when compared with placebo, but demonstrated that the effect of nalbuphine was less marked than that of morphine in delaying recovery. Shah and his colleagues had to remind the patients frequently to record their time to first flatus, because of drowsiness. In our study, two initial measurements (20%) in the nalbuphine group would have been missed as a result of the patients being asleep. This would reduce the sensitivity of TFF, and necessitate using larger groups in a trial using patient assessment of time to first flatus. However, when the patients did report an episode of flatus, it invariably agreed well with the TFF as recorded by the carbon dioxide analyser. This suggests that reliance on reporting by the patient is acceptable.

This trial assessed also the feasibility of using a carbon dioxide monitor as an objective measurement of the passage of flatus; this proved effective and practicable. The carbon dioxide content of human flatus is between 5 and 80%, a high concentration being especially associated with a diet rich in vegetables (Calloway, 1968). The concentration registered by the analyser was considerably lower than this as a result of dilution of the sample by air. Tracings showed little background noise and, invariably, the first deflection registered agreed very closely with the patient's own estimate of first passage of flatus. The technique would be sensitive enough to detect 1 ml of flatus, even with the lowest reported carbon dioxide concentration (5%), so that it is unlikely, with the sampling tip close to the anus, that flatus would be missed. Although the technique failed in two early patients in the placebo group becaue of kinking of the sampling tube, this was corrected easily by using a more rigid catheter for the rest of the trial.

Interpretation was easy and this apparatus could be useful for both research and clinical purposes. For instance, it could be valuable to have an automatic, recorded indication when enteral nutrition may be started following surgery in neonates and infants, and in the ITU in sedated, paralysed or comatose patients, all of whom would be unable to report the passage of flatus. This potential application deserves further study.

Morphine depresses co-ordinated bowel function in both the small intestine and colon in man. This effect appears to be dose-dependent and is seen at doses greater than 8 mg of i.m. morphine

(Adler, Atkinson and Ivy, 1942). Other opioid agonists and agonist–antagonists, such as pethidine and pentazocine, also produce qualitatively similar effects upon bowel motility, although there are quantitative differences (Vaughan Williams, 1954; Danhof, 1967). In the previous study (Shah, Rosen and Vickers, 1984), i.m. morphine and nalbuphine both produced a marked delay in TFF, although the effect of morphine was greater. This study has demonstrated that an i.v. bolus of nalbuphine significantly prolongs TFF in a group of elderly patients who had undergone minor surgery. Adding the recovery time (table I) to the time to first flatus shows that nalbuphine resulted in flatus appearing after about 4.5 h, compared with at 2 h for the placebo. In the study by Shah, Rosen and Vickers (1984), a similar dose of nalbuphine given i.m. resulted in a similar delay (5.65 h) whereas i.m. morphine delayed passage of first flatus by 11.84 h. This suggests that nalbuphine, especially when given i.v., will have considerably less adverse effect on recovery of bowel function than morphine.

The effect of drugs on recovery of bowel function is obviously important when choosing an analgesic for use after abdominal surgery. Further investigations of other drugs will provide useful information, and the technique described enables simple, non-invasive monitoring of bowel motility to assist these studies.

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VARIATIONS IN LUNG VOLUME AND COMPLIANCE DURING PULMONARY SURGERY

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Many factors affect pulmonary function during surgery on the lung. The consequences on lung volume, ventilatory mechanics and the distribution of ventilation between the lungs when turning the patient to his side are well documented. Thus, the FRC of the upper lung increases markedly, while that of the dependent lung decreases somewhat. If intermittent positive pressure ventilation is used, the greater fraction of tidal volume is directed to the upper side, the compliance of which is greater than that of the dependent side (Rehder et al., 1972). Less is known about the changes in lung volume which occur during the operative procedure—those brought about by opening the pleura or by one-lung ventilation. As regards postoperative changes, Lambert, Willauer and Dasch (1955) obtained chest x-rays shortly after lung surgery and found marked signs of impared aeration in the dependent lung, suggesting a reduction in volume. However, to our knowledge, lung volume has not been measured directly at this stage. We measured functional residual capacity (FRC), compliance of the ventilatory system and the distribution of ventilation between the lungs during various phases before, during and after thoracic surgery. Interest was focused primarily on the dependent lung, that is, the lung not undergoing surgery.

SUMMARY

Functional residual capacity (FRC) and breath-by-breath compliance of the ventilatory system (C_{rs}) *were measured in 10 mechanically ventilated patients during anaesthesia for lung surgery (pneumonectomy, lobectomy, lung or pleural resections or exploratory thoracotomy). In eight patients not requiring pneumonectomy, FRC of the lower lung decreased by 8±9% (mean±1 SD)* ($P < 0.05$) *while that of the upper lung increased by 75±24%* ($P < 0.001$) *when the patient was turned to the lateral position. When the pleura was opened, FRC of the lower lung decreased by a further 10±10%* ($P < 0.01$)*. One-lung ventilation (OLV), however, increased FRC of the lower lung back to the value found in the supine position before surgery. When two-lung ventilation was re-established, FRC of the lower lung was about the same as during corresponding stages before OLV. In the two patients who underwent pneumonectomy, FRC of the remaining lung was about 30% greater after OLV than at corresponding stages before surgery. In the patients not requiring pneumonectomy,* C_{rs} *decreased from 29±6 ml/cm* H_2O *to 23±6 ml/cm* H_2O ($P < 0.05$) *on the lower side when the patient was turned on his side. The corresponding figures on the upper side were 24±8 ml/cm* H_2O *and 30±5 ml/cm* H_2O *respectively* ($P < 0.05$)*. There was no further significant change when the pleura was opened. After surgery when the patient was turned to the supine position,* C_{rs} *of the lung not operated on was almost the same as before surgery.*

PATIENTS AND METHODS

Ten patients undergoing elective pulmonary surgery were studied (table I). Any patient with marked impairment of lung function or cardiac decompensation was not included. Patients gave informed consent and the project was approved by the Local Human Studies Committee.

Patients were premedicated with morphine and hyoscine. Anaesthesia was induced with thiopentone. Suxamethonium was given and the trachea was intubated with a Carlens' double lumen tube (Rüsch), size 39 ($n = 6$), 37 ($n = 3$) or 35 ($n = 1$). During one-lung ventilation (OLV) the lumen of the non-ventilated side was left open to the

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TABLE I. *Details of patients studied. FVC = forced vital capacity; $FEV_{1.0}$ = forced expiratory volume in 1 s; M = male; F = female; R = right; L = left*

Patient No.	Sex	Age (yr)	Weight (kg)	Height (cm)	Preop. pulm. function		FRC supine before surgery		Operated side	Diagnosis	Operation
					FVC (litre)	$FEV_{1.0}$ (litre)	R (ml)	L (ml)			
1	F	44	73	168	3.4	2.6	691	765	L	Benign tumour	Wedge resection
2	M	63	84	185	4.3	2.9	1435	1440	R	Squamous carcinoma	Upper lobectomy
3	M	66	69	172	3.9	2.2	—	1191	R	Squamous carcinoma	Exploratory thoracotomy
4	M	50	78	182	2.7	2.3	995	477	L	Pleural mesothelioma	Excision
5	F	31	66	168	3.8	2.3	1245	759	L	Adenocarcinoma	Upper lobectomy
6	F	72	57	154	2.5	1.8	849	689	L	Metastasis from melanoma	Upper lobectomy
7	F	50	60	149	2.8	2.2	806	837	L	Hamarthroma	Lingula resection
8	M	70	81	175	3.0	2.4	904	699	R	Adenocarcinoma	Segmental resection
9	M	63	90	179	4.2	2.4	1102	1046	L	Squamous carcinoma	Pneumonectomy
10	M	71	72	162	2.8	2.1	1156	436	L	Adenocarcinoma	Pneumonectomy

atmosphere. A single dose of alcuronium 10–15 mg was given shortly after tracheal intubation. Anaesthesia was maintained with 50–65% nitrous oxide in oxygen plus intermittent pethidine i.v. The lungs were ventilated by a Servo ventilator 900 C (Siemens–Elema Company). The rate of ventilation was 10–15 b.p.m. and the inspired minute ventilation (ATPD) was 9.0±1.3 litre min^{-1}. This was adjusted at the start of anaesthesia so that end-tidal $P\text{CO}_2$ of the lung not operated on was between 4.0 and 4.5 kPa. Subsequently, it was held constant. However, the rate of ventilation was temporarily increased from 10 to 15 b.p.m. during OLV in three of the patients. Insufflation time was 25–33% and end-inspiratory pause time was 10% of the breathing cycle. A breathing pattern with a constant insufflation flow was used. End-expiratory pressure was zero.

The breathing system is depicted schematically in figure 1. A valve system in the ventilator tubing ensured that expired gas from one lung was directed back to the expiratory port of the ventilator which performed the insufflation. The expired gas from the other lung was directed to the expiratory port of a second Servo ventilator electronically synchronized with the first. Thus, the expired volume from each lung could be measured separately. Since only one ventilator performed the insufflation, the insufflation pressure on both sides was equal. Thus the distribution of the tidal volume between the lungs depended on the resistance and compliance of the two sides. Airway pressure was measured on each side close to the expiratory valve with the standard manometer on the ventilators. Signals representing airway pressure and expired tidal volume were recorded on an ink-jet recorder (Mingograph-81, Siemens–Elema Company). After surgery, there was frequently leakage of gas from the upper lung into the pleural cavity. As a result, the tidal volume of this lung could not be measured directly during these stages. Instead, it was calculated from total inspired tidal volume and measured expired tidal volume of the other lung. Since at least 90 min of anaesthesia had elapsed, we assumed that there was negligible net transport of nitrous oxide into or from the body.

On each side, breath-by-breath compliance of the ventilatory system (C_{rs}) was obtained as $C_{rs} = V\text{T}/P_{\text{pause}}$, where $V\text{T}$ = inspired tidal volume and P_{pause} = pressure at the end of the end-inspiratory pause. The duration of this zero

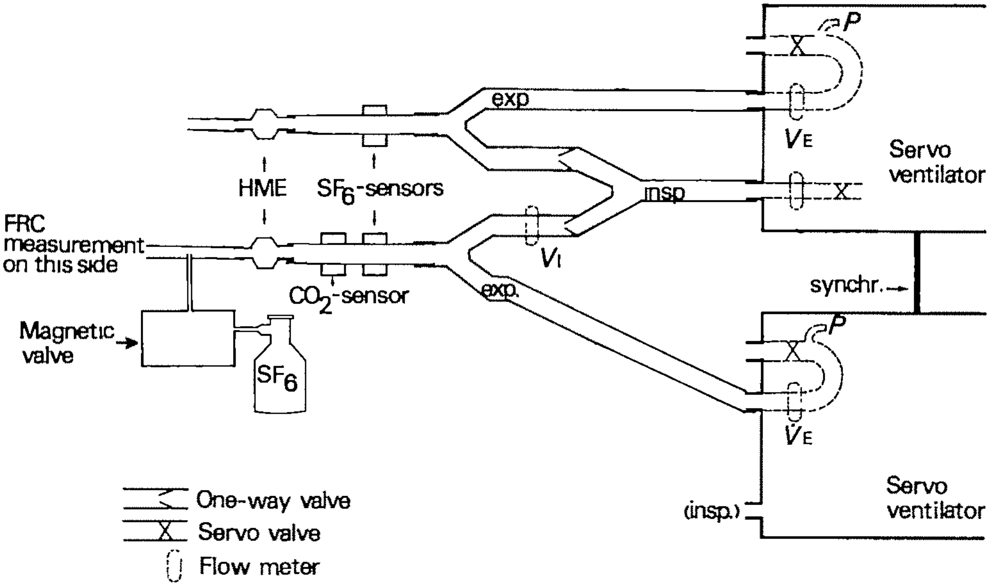

FIG. 1. The measurement system. HME = heat/moist exchanger. Synchr. = synchronization cable. P = tube to pressure transducer.

flow interval was 0.4–0.6 s. In our patients this was adequate to achieve a clearly defined pressure plateau, although Gottfried and colleagues (1985) have found that longer equilibration times are sometimes required in patients with obstructive lung disease. The above formula is strictly valid only if end-expiratory lung pressure and, hence, end-expiratory flow is zero. In the patients not undergoing pneumonectomy the flow had, in fact, ceased at end-expiration during all measurements except OLV. At this stage, end-expiratory flow was 12±9% (mean±1SD) of early expiratory flow. Likewise, in the two patients who underwent pneumonectomy the end-expiratory flow was between 12 and 19% of early expiratory flow after starting OLV. Therefore, we did not calculate compliance when only one lung was ventilated.

Functional residual capacity (FRC) was measured by a multiple breath washout technique using sulphur hexafluoride (SF_6) as tracer gas (Jonmarker, Castor et al., 1985; Jonmarker, Jansson et al., 1985). SF_6 was washed in through a catheter until the alveolar concentration of SF_6 was about 0.5%. This was measured with an SF_6 analyser, the transducer of which was placed over a cuvette in the airway. Signals representing expired flow and SF_6 concentration were fed into a computer (PDP-11, Digital Equipment Corp.) which calculated the FRC. The value was corrected for apparatus deadspace. Duplicate FRC measurements were obtained on each occasion. Figure 1 shows that two SF_6 analysers were used. However, only one was connected to the computer and when it was desired to measure FRC in both lungs, this was done sequentially. The SF_6 analysers had a slightly different design. One was sensitive to carbon dioxide and a CO_2-Analyzer 930 (Siemens–Elema Company) was incorporated to the circuit in order to permit electrical compensation for this. The other SF_6 analyser, a newly delivered prototype, was used only to test the seal between the lungs. This was done by observing the SF_6 signal on one side, while supplying SF_6 to the other side. In addition, the seal was tested by auscultation. As the SF_6 delivery system used at present is able to give only a constant flow of SF_6 during inspiration, it is essential that inspiratory flow is also constant to prevent variations in the inspiratory SF_6 concentration. Although we used a breathing mode with constant insufflation flow the possibility remained that, since the inspiratory gas was distributed freely between the two lungs, flow into each lung could vary during inspiration. To assess this, a flow meter (Siemens–Elema 6395 420) was placed close to the Y-piece on the side on which FRC was measured (fig. 1). Signals from the flow meter were recorded on the Mingograph and the maximum deviation between instantaneous inspiratory flow velocity and the mean inspiratory flow velocity was calculated from the curve during the various phases. The deviation was 6 ± 6% of mean flow velocity (mean ± 1 SD). This was considered acceptable.

The resistance to flow in the Carlens' tube and its connections up to the Y-piece was tested *in vitro*. The decrease in pressure over the left lumen at a flow of 0.5 litre s^{-1} was 1.58, 1.05 and 0.96 kPa for tube sizes 35, 37 and 39, respectively. The corresponding figures for the right lumen were 1.40, 0.98 and 0.94 kPa. The compliance of the whole tubing system was 10.5 ml kPa^{-1}. Apparatus deadspace, including the heat/moisture exchanger, was about 45 ml on each side. The flow meters of the ventilators were calibrated daily with 50% nitrous oxide in oxygen using a wet gas meter (Flonic, Schlumberger). It was confirmed separately that the changes in inspired oxygen concentration that took place during anaesthesia (between 35 and 50%) did not appreciably alter the measurement of volume. The ventilator manometer was calibrated with a mercury manometer. A factor of 1.09 was used to convert expired volume and FRC from ATPS to BTPS.

The measurements were made at seven stages: (1) before surgery, supine position; (2) before surgery, lateral position, 90°; (3) after opening the pleura; (4) during OLV; (5) after OLV, before closing the pleural cavity; (6) after surgery, lateral position; (7) after surgery, supine position.

During stages 1 and 2, FRC and compliance were measured on both sides. During the remaining stages, time permitted FRC measurements only on the dependent side. It would in any case have been difficult to obtain meaningful measurements from the operated lung after OLV because leaks into the pleural cavity were usually present. Surgery was discontinued during the measurements.

Statistics

The two-sided Student's test for paired observations was used. Probability values less than 0.05 were considered to indicate statistical significance.

RESULTS

Morphometric data, preoperative lung function, initial FRC during anaesthesia, diagnoses and extent of surgery are shown in table I. Forced vital capacity was 81 ± 15% of predicted and $FEV_{1.0}$ was 80 ± 15% of predicted (Berglund et al., 1963; Birath, Kjellmer and Sandquist, 1963). Consequently, $FEV_{1.0}/FVC$ was close to the expected value (99 ± 16%). One-lung ventilation was performed in eight of the patients. Surgery lasted 1.9 ± 1.2 h and anaesthesia 4.7 ± 1.2 h. The measurements prolonged anaesthesia by about 1 h.

Patients who did not undergo pneumonectomy (n = 8) (fig. 2)

FRC. In the lung not to be operated on, FRC decreased 8 ± 9% (mean ± 1 SD) ($P < 0.05$) when the patient was turned from the supine to the lateral position. In the other (upper) lung, FRC increased by 75 ± 24% ($P < 0.001$). In the dependent lung, FRC decreased further when the pleura was opened, but when OLV was established ($n = 6$), FRC increased again. At this stage FRC was 3 ± 12% greater (ns) than in the supine position before surgery. When bilateral lung ventilation was reinstituted, FRC in the dependent lung decreased to about the same value as before OLV. Likewise, after closing the pleural cavity, the values were similar to those observed before the pleura was opened. In the supine position after surgery, FRC of the lung not operated on was 10 ± 15% greater (ns) than in the supine position before surgery.

Compliance of the ventilatory system (C_{rs}). When the patient's position was changed from supine to lateral, C_{rs} of the dependent side decreased from 29 ± 6 ml/cm H_2O to 23 ± 6 ml/cm H_2O while C_{rs} of the upper side increased from 24 ± 8 ml/cm H_2O to 30 ± 5 ml/cm H_2O. Opening the pleural cavity caused no significant change in C_{rs} of the dependent side, but closing the chest resulted in a significant decrease in C_{rs} to 20 ± 4ml/cm H_2O. When the patient was turned back to the supine position, C_{rs} of the side not operated on increased to 27 ± 6ml/cmH_2O; that is, it was nearly the same as in the supine position before surgery.

Distribution of the tidal volume between the lungs. The fraction of the tidal volume going to the lower lung decreased from 53 ± 6 to 44 ± 6% when the patient was turned from the supine to the lateral position. No further change appeared when the pleural cavity was opened. After OLV, when the pleural cavity had been closed and the operation was finished, there was a slight increase in the fraction of ventilation to the lower lung. During the final measurement (supine position), the lower lung received 63 ± 11% of the minute ventilation,

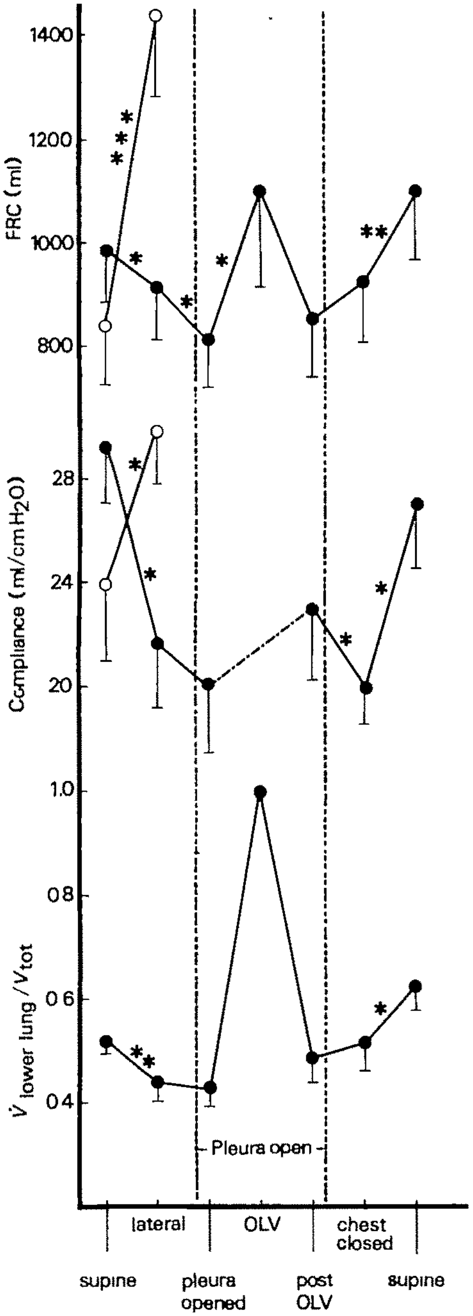

FIG. 2. FRC, compliance of the ventilatory system and fraction of ventilation to the lower lung in patients who did not undergo pneumonectomy. Eight patients, except during OLV ($n = 6$). Mean values and 1 SEM. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$. ○ = Lung operated on; ● = other (lower) lung.

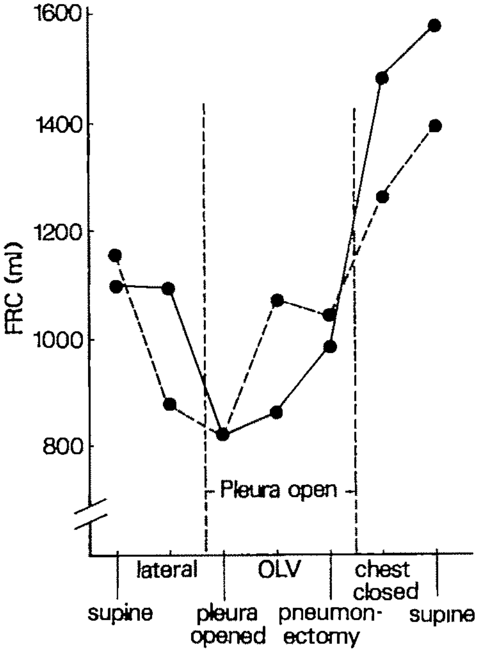

FIG. 3. Changes in FRC of the remaining right lung in two patients undergoing pneumonectomy.

which was not significantly different from the value obtained before surgery.

Patients who underwent pneumonectomy (n = 2) (fig. 3)

The findings in respect of FRC and C_{rs} were similar to those in the other patients, except that FRC of the remaining lung was greater after pneumonectomy than at corresponding stages before surgery.

DISCUSSION

The method for measuring FRC was chosen specifically because it is convenient to use in the operating room during nitrous oxide in oxygen anaesthesia. The accuracy and reproducibility of the method have been discussed previously (Jonmarker, Castor et al., 1985; Jonmarker, Jansson et al., 1985).

A limitation of the FRC measuring system currently in use is that it requires a constant insufflation flow. This is because, at present, the system is able to deliver only a constant flow of SF_6 through the thin catheter (fig. 1) during insufflation. If inspired flow varies, the SF_6 concentration of the inspired gas will also fluctuate and not yield a uniform alveolar concentration of SF_6. Fortunately, the inspiratory flow to each lung was almost constant in the present study.

Regional variations in the uptake of nitrous oxide constitute another source of error, since this will cause alveolar SF_6 concentration to be non-uniform, even with constant inspired SF_6 concentration. The problem is probably of minor importance since about 200 ml min^{-1} of nitrous oxide, that is only 3–4% of the alveolar minute ventilation, is taken up after 15 min of breathing a 75% nitrous oxide mixture (Beatty, Kay and Healy, 1984). Longer exposure reduces the uptake but, on the other hand, uptake may possibly have been accentuated by opening of the pleural cavity (Weatherill et al., 1984). One factor which may have limited the impact of nitrous oxide uptake as a source of error is that alveolar concentration of SF_6 at the end of wash-in was obtained as the mean value over a large fraction of the expiration, *viz.* the final half of the volume (Jonmarker, Jansson et al., 1985). Furthermore, uptake of nitrous oxide ceases when alveolar nitrous oxide tension approaches mixed venous tension. The latter tension increases rapidly after the patient starts to inhale nitrous oxide and this sets a lower limit below which local nitrous oxide tension cannot decrease. This will in turn reduce the scope for variations in alveolar SF_6 concentration. In contrast, mixed venous oxygen tension is always much less than inspired oxygen tension, which should allow for greater regional variation in alveolar oxygen tension. Possibly, therefore, differential oxygen uptake with consequent variation in alveolar SF_6 concentration may have constituted a problem at least as important as nitrous oxide uptake. Differential oxygen uptake is, of course, a general problem which occurs also during oxygen–air breathing and with tracer gases other than SF_6.

When the patient was turned from the supine to the lateral position, FRC, C_{rs} and the fraction of total ventilation decreased slightly on the lower side while, on the upper side, the same indices (particularly FRC) increased (75±24%). This is in agreement with other studies in mechanically ventilated subjects (Rehder et al., 1972; Baehrendtz and Klingstedt, 1984; Hedenstierna et al., 1984). The probable cause of these changes is that the lower lung is compressed by the weight of the mediastinum and by the elevation of the diaphragm (Froese and Bryan, 1974). In the present study, FRC of the lower lung decreased further when the pleural cavity was opened, presumably because of a shift downwards of the unsupported mediastinum. We did not measure FRC in the upper lung at this stage, but both theory and direct observation in the wound tell us that FRC decreased also in this lung. The decrease in lung volume when the pleura is opened is consistent with the study by Kerr and co-workers (1974) who found an increase in venous admixture at this point. However, both in their study and in a study from our hospital (Werner et al., 1984), the impairment in arterial oxygenation appeared to be clinically unimportant. Zero end-expiratory pressure was used in both these studies, as in the present one.

During OLV, mean FRC of the non-operated lung increased to about the same value as in the supine position before surgery. An explanation for the increase is that the lung did not have enough time to deflate during expiration, despite the fact that it lasted about 3 s. The explanation is supported by the finding of an appreciable airway flow at the end of expiration (12±9% of early expiratory flow). The high resistance to gas flow in the Carlens' tube and the fact that the whole of the minute volume was directed to the lower lung during OLV probably contributed to the delayed emptying. Many studies (Khanam and Branthwaite, 1973; Aalto-Setälä, Heinonen and Salorinne, 1975; Capan et al., 1980; Katz et al., 1982) have shown that PEEP during OLV has either a harmful or no effect on arterial oxygenation. We suggest that this is because the dependent lung is adequately expanded already without PEEP. Thus, the harmful effects of selective PEEP to the dependent lung—diversion of blood flow from the ventilated lung to the collapsed upper lung—dominate over the beneficial effects.

In the patients undergoing pneumonectomy, FRC of the dependent lung increased markedly after the pneumonectomy. This is partly explained by the same mechanism as outlined above for the FRC increase during OLV. Another factor is that −5 to −8 cm H_2O of pressure was applied to the empty pleural cavity via the pleural drains. This is less than pressures normally prevailing in the pleura at end-expiration during controlled ventilation (about −3 cm H_2O (Nunn, 1977)).

Despite the fact that most of the effect of the single dose of neuromuscular blocking drug (alcuronium) must have worn off, we found that FRC and compliance of the non-operated side had not decreased after surgery in comparison with corresponding measurements made before surgery. This result is consistent with findings by Kerr and colleagues (1974) and by Katz and co-workers (1982), neither of whom found any impairment of arterial oxygenation after lung surgery. Superficially, the present finding that FRC of the non-operated lung was maintained after surgery, is contradicted by x-ray studies in which pictures taken in the lateral decubitus position shortly after surgery showed marked changes in the dependent lung. However, both Lambert, Willauer and Dasch (1955) and Potgieter (1959) found that these changes resolved shortly after the patient was placed supine. Craig, Bromley and Williams (1962) found areas of increased opacity in the lung fields in patients undergoing closed mitral commisurotomy, but in only four out of 49 patients who had undergone lung or pleural surgery.

We conclude that FRC and compliance of the non-operated side vary markedly during lung surgery, but that the changes are reversible.

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INFLUENCE OF BOLUS DOSES OF PHENOPERIDINE ON INTRACRANIAL PRESSURE AND SYSTEMIC ARTERIAL PRESSURE IN TRAUMATIC COMA

R. M. BINGHAM AND C. J. HINDS

Narcotic analgesics are administered commonly to those patients in traumatic coma requiring mechanical ventilation—to provide analgesia (particularly in the presence of multiple injuries) and to suppress spontaneous, asynchronous ventilatory movements. Since the maintainance of cerebral perfusion pressure (CPP) is fundamental to successful management in such patients, the influence of narcotics on intracranial pressure (ICP) and mean arterial pressure (MAP) is of particular relevance.

Although a number of investigations have suggested that narcotics have little effect on ICP (Barker et al., 1968; Fitch et al., 1969; Misfeldt et al., 1976), these were performed on patients undergoing elective neurosurgical procedures, in many of whom ICP was normal, whereas in others intracranial hypertension was secondary to focal space-occupying lesions. Consequently, the results of these studies may not be directly applicable to patients with severe head injury. This view is supported by a recent case report which described significant increases in ICP following the administration of bolus doses of phenoperidine i.v. to a patient in traumatic coma (Grummitt and Goat, 1984).

The purpose of this study was to examine further the influence of i.v. bolus doses of the narcotic analgesic phenoperidine on ICP, mean arterial pressure and cerebral perfusion pressure in head-injured patients.

SUMMARY

The effects of bolus doses of phenoperidine 1–2 mg i.v. either alone, or combined with pancuronium 2–4 mg, were investigated in seven patients in traumatic coma. Phenoperidine alone significantly reduced mean arterial pressure (MAP) by a mean (±SEM) of 13.2(±2.8) mm Hg. Overall there was no significant change in intracranial pressure (ICP) despite the decreases in MAP and, consequently, cerebral perfusion pressure (CPP) decreased (14.0±2.4 mm Hg) on all but one occasion. In some instances these decreases were considerable (maximum 38 mm Hg). Similar results were obtained when phenoperidine was combined with pancuronium. These findings suggest that the bolus administration of phenoperidine and probably other opiates should be avoided in traumatic coma.

PATIENTS AND METHODS

Patients

Seven consecutive patients (two female) admitted to the Intensive Care Unit with severe head injury (Glasgow Coma Score < 8) were studied. Their ages were in the range 11–37 yr. Evacuation of intracranial haematoma was performed in three patients (one intracerebral, one extradural, one subdural). Three had diffuse swelling and the remaining patient had predominantly left hemisphere oedema.

Monitoring

Indwelling Teflon cannulae were placed in a radial artery and in the right internal jugular vein

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and used to monitor, respectively, arterial and central venous pressure (CVP) continuously (Bell and Howell type 4/327/1 pressure transducers). A pre-calibrated subdural pressure transducer which can be zeroed *in situ* (Gaeltec Ltd) was used for the continuous monitoring of ICP.

All monitoring equipment was zeroed and calibrated at least twice a day and more frequently, if necessary. A continuous record of CVP, MAP and ICP was obtained on a Devices M19 4-channel chart recorder (with three 3559 transducer amplifiers for the pressure channels.)

Clinical management

All patients received intermittent positive pressure ventilation to maintain Pa_{CO_2} between 3.4 and 4.7 kPa. Inspired oxygen concentration was adjusted to maintain arterial oxygen saturation greater than 90%.

Patients were sedated using a continuous i.v. infusion of etomidate (initially 5 µg kg^{-1} min^{-1}) supplemented with bolus doses to control any acute increases in ICP, and before stimulating procedures. Phenoperidine 1–2 mg i.v. with or without pancuronium 2–4 mg i.v. was administered, if necessary, to prevent the patient resisting the ventilator. Mannitol 0.3 g kg^{-1} every 6 h was also used to control ICP. However, if on any occasion the ICP failed to decrease following the administration of mannitol, its use was discontinued. All but two patients received a dose of mannitol at some stage during their treatment and four required repeated administrations.

Fluid intake was restricted to 5% dextrose 1 ml kg^{-1} h^{-1}. Colloidal solutions (Haemaccel or plasma protein fraction) were administered, as required, to maintain the circulating fluid volume. Prophylactic anti-convulsant therapy (phenobarbitone 60 mg i.m. 8-hourly in adults) was given to all patients (supplemented with diazepam and phenytoin if seizures occurred).

All events, drug administrations and procedures were noted on the 4-channel chart recording, which was continued for the duration of ICP monitoring (up to 7 days). The effects of bolus doses of phenoperidine (with or without pancuronium) on ICP and MAP were determined by retrospective analysis of the chart records. Analysis was restricted to those occasions when the bolus doses were not accompanied by the administration of any other drug nor by any stimulating procedure. Statistical comparisons were performed using the two-sample *t* test.

RESULTS

Bolus doses of phenoperidine, with or without pancuronium, induced significant decreases in MAP (mean(±SEM) = 16.6(±4.3) mm Hg ($P < 0.005$) and 13.2(±2.8) mm Hg ($P < 0.0001$), respec-

TABLE I. *Mean changes (±SEM) in MAP, ICP and CPP following bolus doses of phenoperidine(±pancuronium)*

	Phenoperidine alone (n = 16)	Phenoperidine with pancuronium (n = 18)
ΔMAP (mm Hg)	−13.2 (±2.8)	−16.6 (±4.3)
ΔICP (mm Hg)	+0.81 (±1.4)	+1.89 (±2.1)
ΔCPP (mm Hg)	−14.0 (±2.4)	−18.4 (±3.6)

TABLE II. *Changes in MAP, ICP and CPP (mm Hg) following individual bolus doses of phenoperidine with and without pancuronium*

Change in MAP (mm Hg)	Change in ICP (mm Hg)	Change in CPP (mm Hg)
Phenoperidine alone		
−13	0	−13
−5	7	−13
−14	11	−25
−50	−12	−38
−13	4	−17
−18	10	−28
−5	1	−6
−8	3	−11
−8	1	−9
0	0	0
−8	−1	−7
−10	−2	−8
−20	0	−20
−13	−2	−11
−11	−3	−8
−15	−4	−11
Phenoperidine with pancuronium		
−7	1	−8
7	1	6
−13	−4	−9
2	1	1
−30	−2	−28
−25	−7	−18
−65	−14	−51
−49	−7	−42
−25	−8	−17
−17	1	−18
−13	12	−25
−5	22	−27
−14	15	−29
−20	11	−31
−18	6	−24
−3	0	−3
−3	4	−7
0	2	−2

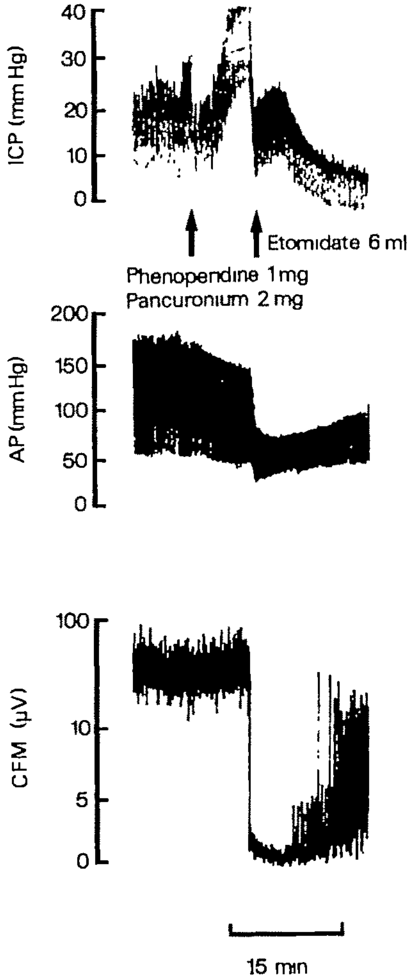

FIG. 1. Examples of the effects of a phenoperidone bolus and an etomidate bolus on ICP and arterial pressure (AP) in the absence of external stimulation. The phenoperidine bolus is followed by an increase in ICP and moderate hypotension: CPP decreases. An attempt to treat the increase in ICP with etomidate was successful at the expense of marked hypotension which resulted in a further reduction in CPP. Note the marked depression of the CFM (cerebral function monitor) associated with the administration of etomidate.

tively) (table I). MAP decreased on 15 of 16 occasions following phenoperidine alone (on one occasion MAP was unchanged) (table II), and 15 of 18 occasions following phenoperidine combined with pancuronium. In this latter group MAP increased slightly on two occasions and remained unchanged on a third.

Despite the decreases in MAP, ICP increased slightly in both groups (0.8(±1.4) mm Hg after phenoperidine alone and 1.9(±2.1) mm Hg after phenoperidine combined with pancuronium). Seven of the 16 bolus doses of phenoperidine alone and 11 of the 18 bolus doses of phenoperidine combined with pancuronium were followed by an increase in ICP of between 1 and 22 mm Hg.

As a result of these changes in ICP and MAP, CPP was reduced significantly overall by 14.0(±2.4) mm Hg after phenoperidine alone ($P < 0.0001$) and by 18.4(±3.6) mm Hg after phenoperidine and pancuronium combined ($P < 0.0001$) (table I, fig. 1). CPP was unchanged on one occasion after the administration of phenoperidine alone, and on two occasions slight increases in CPP, secondary to unexplained increases in MAP, followed the administration of phenoperidine combined with pancuronium. All the remaining bolus doses of phenoperidine (with or without pancuronium) decreased CPP.

In both groups very large decreases in CPP were occasionally identified (maximum of 38 mm Hg with phenoperidine alone, and 51 mm Hg with phenoperidine and pancuronium combined). These were usually associated with marked hypotension (MAP decreased by 50 mm Hg and 65 mm Hg in the above examples). There were no significant differences between the changes in MAP, ICP or CPP between the two groups.

DISCUSSION

In this study, the administration of phenoperidine virtually always resulted in a decrease in MAP. ICP did not decrease correspondingly; indeed, it was usually unchanged, or even increased, and cerebral perfusion pressure was, therefore, decreased. In this respect there was no difference between the effects of phenoperidine alone or phenoperidine combined with pancuronium. These results are in agreement with the observations of Grummitt and Goat (1984), who suggested that phenoperidine may actively increase cerebral blood flow (CBF), and therefore ICP, by inducing cerebral vasodilatation.

The results of experimental studies of the effects of narcotic analgesics on CBF are conflicting and there are marked species differences (Nilsson and Ingvar, 1965; Michenfelder and Theye, 1971). One human study, in which phenoperidine was combined with droperidol, found no detectable effect of this combination on CBF (Barker et al., 1968).

Most clinical studies, however, have concentrated on the effects of narcotics on ICP. In spontaneously breathing subjects given opiates, ICP is increased secondary to ventilatory depression and hypercapnia, but when the arterial carbon dioxide tension is maintained constant the results are variable. Fitch and colleagues (1969) found that the administration of fentanyl and droperidol to patients with or without intracranial hypertension significantly reduced ICP. In the former group, however, CPP was reduced as a consequence of associated arterial hypotension. In the same study there was no significant reduction in ICP following phenoperidine combined with droperidol in patients with normal CSF pathways. This finding led the authors to postulate that there was a difference between the effects of fentanyl and phenoperidine on CBF and cerebral metabolic rate. Similar results were obtained by Moss and co-workers (1978), who studied the combination of fentanyl and droperidol. Although the changes in ICP were small, CPP always decreased—on two occasions to less than 50 mm Hg. In contrast, Misfeldt's group found that fentanyl (also combined with droperidol) increased ICP in five of eight patients; CPP was again reduced in all patients (Misfeldt et al., 1976). Finally, Barker and colleagues (1968) found that CSF pressure was unchanged following the administration of phenoperidine and droperidol.

These findings may not, however, be applicable to patients with severe head injuries, since they were all performed on patients with focal intracranial lesions before elective neurosurgical procedures. In many of these patients ICP was normal and intracranial compliance may have been sufficient to allow some increase in intra-cranial volume without change in ICP. Furthermore, the narcotics were commonly given following the induction of anaesthesia with a barbiturate and the institution of controlled ventilation, both of which are likely to have attenuated any subsequent increases in ICP. In addition, they were always given in combination with droperidol which is known to be a cerebral vasoconstrictor (Michenfelder and Theye, 1971).

The explanation for the increases in ICP associated with more than half of the bolus doses of phenoperidine in our patients is uncertain. It is possible that, as Drs Grummitt and Goat suggest, phenoperidine results in active cerebral vasodilatation. Alternatively, however, cerebral vasodilatation may occur as an autoregulatory response to arterial hypotension, in which case cerebral blood flow might be maintained despite the reduction in CPP. Whatever the mechanism of the ICP changes, the arterial hypotension which almost always followed the administration of phenoperidine is likely to be detrimental in this group of patients. It is conceivable that analgesia would be better provided in such patients by the continuous infusion of an appropriate narcotic analgesic.

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EFFECT OF STRETCH EXERCISES ON SUXAMETHONIUM INDUCED FASCICULATIONS AND MYALGIA

D. A. MAGEE AND R. J. S. ROBINSON

SUMMARY

Muscle fasciculations and pain following the administration of suxamethonium were assessed in a group of patients who performed a series of stretch exercises approximately 1 h before operation. Comparison was made with a group who received suxamethonium but no pretreatment. Fasciculations were significantly reduced in the exercised group, and the incidence of muscle pain decreased from 52% in the untreated group to 12% in the exercised group. A significant relationship was shown between the severity of visible fasciculations and muscle pain.

The speed of onset of blockade and the excellent intubating conditions achieved with suxamethonium are frequently counteracted by muscle fasciculations, increases in intragastric and intraoccular pressures (Famewo, 1981) and postoperative muscle pain. Since Churchill-Davidson demonstrated the modifying influence of pretreatment with gallamine in 1954, many forms of pretreatment have been shown to decrease the incidence of these side effects (table I), although none abolishes them totally. Investigation is made more complex since muscle pain is affected by many factors, including the time of ambulation (Churchill-Davidson, 1954), site of surgery (Brodsky and Ehrenwerth, 1980), age (Bush and Roth, 1961), pregnancy (Thind and Bryson, 1983), sex (Riding, 1975), and degree of physical fitness (Newnam and Loudon, 1966).

Stretch exercises performed by athletes before physical effort have the effect, among other things, of decreasing muscle damage during, and diminishing muscle pain after, the actual exercise (Harris, 1984). The aim of this study was to apply stretch exercises to patients undergoing anaesthesia requiring tracheal intubation to determine whether a decrease in the incidence of suxamethonium-induced muscle pain could be achieved.

PATIENTS AND METHODS

The approval of the hospital ethics committee was obtained and each patient gave informed consent before participation. Fifty patients (ASA Class I) presenting for routine minor surgery, and who were expected to be ambulatory on the evening of surgery, were investigated. Subjects were randomly divided into an exercise and a control group. Subjects in the exercise group performed a series of stretch exercises under the supervision of one of the authors (D. M.). The exercises were designed to give a slow, prolonged and repetitive stretching of the muscles of the neck, shoulder

TABLE I. *Pretreatment agents shown to modify suxamethonium-induced fasciculations or muscle pain, or both*

Agent	Author	Year
Gallamine	Churchill-Davidson	1954
Tubocurarine	Cullen	1971
Self-taming	Baraka	1977
Dantrolene	Collier	1979
Thiopentone	Manani and colleagues	1981
Fazadinium	Famewo	1981
Lignocaine	Fassoulaki and Kaniaris	1981
Diazepam	Verma	1982
Vecuronium	Ferres and colleagues	1983
Fentanyl	Lindgren and Saarnivaara	1983
Calcium gluconate	Shrivastava and colleagues	1983

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TABLE II. *Grading of fasciculations (Fry, 1975)*

Grade	Description
I	Absent or minimal fasciculations: movements of tongue, corner of mouth or individual digits only.
II	Moderate fasciculations: facial grimace, movement of hand or rotation of arm.
III	Severe fasciculations: visible displacement of head or whole limb.
IV	Maximal fasciculations: purposeful-seeming movement of limb, or generalized clonic contractions.

TABLE III. *Sex and age distribution of the groups*

			Age (yr) Mean (SD)	
Group	M	F	M	F
Exercised	10	15	30.2 (13.3)	35.5 (11.5)
Control	11	14	30.7 (12)	33.6 (11.7)

girdle, chest and abdomen. The exercises, which lasted approximately 15 min, were performed just before premedication, and are more completely described in the Appendix.

Each patient was pre-medicated with atropine and a narcotic analgesic 1 h before surgery. Anaesthesia was induced with thiopentone 4.5 mg kg^{-1}, followed immediately by suxamethonium 1.5 mg kg^{-1} given over 5 s. After tracheal intubation, anaesthesia was maintained with nitrous oxide in oxygen supplemented with a volatile anaesthetic agent.

Following the administration of the suxamethonium, muscle fasciculations were graded, according to the scale devised by Fry (table II), by the consultant anaesthetist administering the anaesthetic, who was unaware of the subject's treatment group. Each patient was interviewed on the first and second days after operation and was asked to complete a standard questionnaire, the third question of which was "Do you have or have you had any pain in your muscles following your operation?"

The differences between groups were compared using the chi square test or Student's t test for independent samples. Spearman's rank correlation co-efficient was calculated to test the relationship between exercise, age, sex, the degree of fasciculation, and the presence or absence of muscle pain.

RESULTS

Table III shows the age and sex distribution of the two groups, and the incidence of muscle fasciculations and postoperative muscle pain are given in figure 1. There were no significant differences between the treatment and control groups in the distribution of sexes or mean age. Treated subjects showed significantly less severe muscle fasciculations ($P < 0.001$) and reported postoperative muscle pain less often than control subjects ($P < 0.001$). The incidence of muscle pain was significantly influenced by the severity of fasciculations ($P < 0.01$). The intensity of muscle fasciculation was significantly greater in female

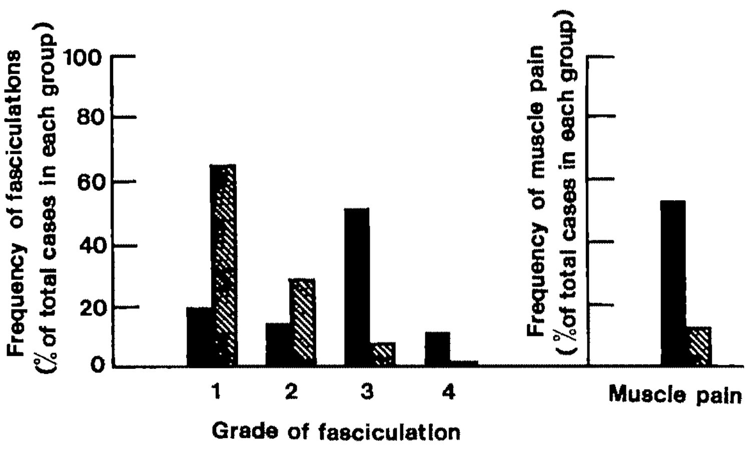

FIG. 1. Overall frequency of fasciculations and muscle pain in control (■) and exercised patients (▨).

patients ($P < 0.01$), and female subjects had significantly more postoperative muscle pain ($P < 0.01$). There was no relationship between the age of the subjects and either the degree of muscle fasciculation or the presence of postoperative muscle pain.

While conditions for intubation were not specifically investigated, there were no apparent differences between the two groups of patients, and muscle paralysis appeared to be uniformly excellent.

DISCUSSION

The continuing interest in new methods of preventing suxamethonium-induced fasciculations and muscle pain reflect both the importance of suxamethonium in clinical practice and the difficulty in preventing these side effects. This study has shown that stretch exercises significantly reduced the incidence of both fasciculations and postoperative muscle pain.

Harris (1984) has shown that muscles are mechanically fatigued and unresponsive following stretch exercises. Muscle tone can be diminished by slow stretching of the muscle where the stretch is maintained over a period of time. The muscle stretch receptors are progressively desensitized as the receptor potential adapts under conditions of prolonged slow stretch. In this way stretch exercises regulate alpha motor neurone discharge through a reduction in the rate of gamma efferent discharge from the muscle spindle. The resulting decrease in muscle tone and increased mechanical fatigue may increase the threshold for motor units, thus altering the action of suxamethonium.

Kitamura and colleagues (1981) have suggested that muscle fasciculations are caused because suxamethonium releases acetylcholine from the prejunctional nerve terminal. In the time interval between stretch exercising and suxamethonium injection (approximately 1 h) there is clearly ample time for regeneration of acetylcholine, since acetylcholine reservoirs are replenished within 3–5 min after rapid exercise (Foldes et al., 1961).

Waters and Mapleson (1971) attributed suxamethonium-induced muscle pain to the development of shearing forces between muscle and fascia. Stretch exercises decrease muscle tone and cause stretch of fibrous tissue (Harris, 1984) and this combination may prevent the development of shearing forces sufficient to damage the connective tissue elements. Waters and Mapleson also showed that there was no relationship between the severity of visible muscle fasciculations and the development of muscle pain, and this finding is confirmed by the results of other workers (Newman and Loudon, 1966; Ferres et al., 1983). This suggests that pretreatment with non-depolarizing myoneural blocking drugs may reduce the incidence of visible fasciculations and muscle pain in different groups of patients. The relationship shown in this study between fasciculations and muscle pain is presumably a consequence of stretch exercises, and the significance of this finding in relation to pretreatment with non-depolarizing neuromuscular blocking agents is not clear.

The increased intensity of fasciculations and the higher incidence of muscle pain in female patients shown here is in agreement with the early findings of Churchill-Davidson (1954) and with subsequent reports (Riding, 1975).

The reported frequency of muscle pain following suxamethonium varies from 1.5% (Crawford, 1971) to 85% (Foster, 1960). Ferres and co-workers (1983) reported an incidence of 41%, which decreased to around 20% after pretreatment with various non-depolarizing neuromuscular blocking agents. Our figures shown an overall frequency of 52%—which decreased to 12% following stretch exercises. The advantages of stretch exercises over pretreatment with non-depolarizing neuromuscular blockers include the avoidance of partial antagonism of the depolarizing blockade, the avoidance of muscle weakness and diplopia, and the avoidance of the theoretical possibility of the development of a mixed neuromuscular blockade.

The major difficulty in the routine application of stretch exercises lies in the time taken, and the personnel required for their supervision. The positive acceptance by patients of these exercises suggests that a high degree of compliance might be achieved by distribution of a simple illustrated leaflet, together with appropriate encouragement by the anaesthetist, to perform the exercises at the time of premedication.

The interval between pretreatment with non-depolarizing neuromuscular blockers and the administration of suxamethonium has been shown to be of importance (Riding, 1975). This study has not examined the time relationship of stretch exercises to suxamethonium administration. A further study is proposed to examine this relationship and to compare the effectiveness of stretch exercises with pretreatment using non-depolarizing neuromuscular blocking agents.

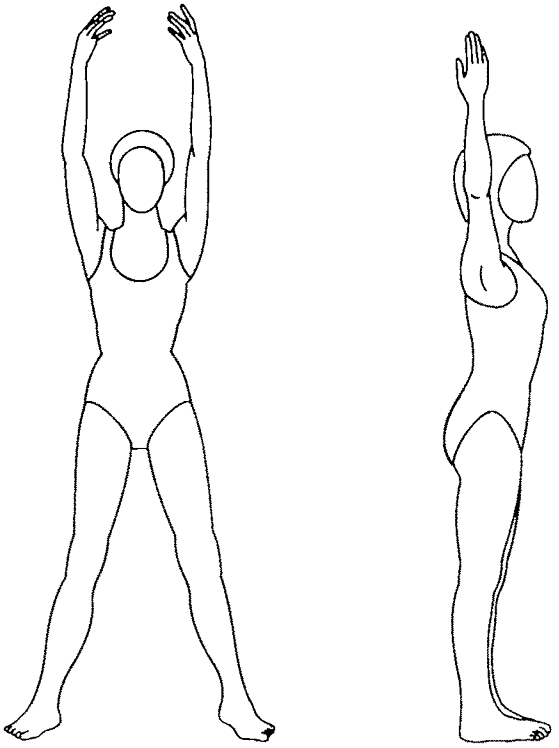

FIG. 2. Shoulder stretch.

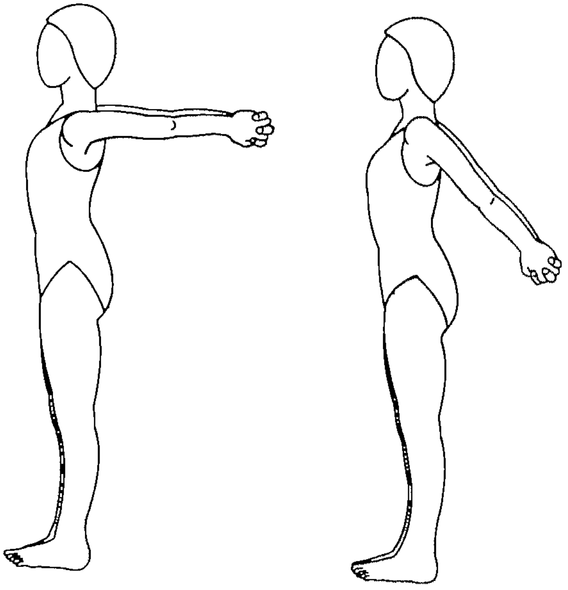

FIG. 3. Anterior shoulder stretch.

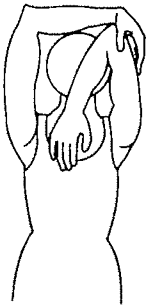

FIG. 4. Posterior shoulder stretch.

APPENDIX

These instructions were given to patients in the exercise group. Supervision of the exercises was maintained to ensure comprehension of the instructions and compliance.

(1) *Shoulder stretch* (fig. 2). With feet apart extend your arms in front of your body, fingers interlaced. Turn your grip, so that your palms face away from the body, and raise straight arms overhead, forcing them into as much hyperextension as possible. Hold this position for five seconds and then relax for five seconds.

Repeat five times.

(2) *Anterior shoulder stretch* (fig. 3). With feet apart, interlace your fingers behind your back, and slowly force your arms upwards and backwards as far as possible. Hold this position for five seconds and relax for five seconds.

Repeat five times.

(3) *Posterior shoulder stretch* (fig. 4). Place your hand behind your neck and with the other hand on your elbow contract by forcing your elbow into your hand. Hold for five seconds and relax gently, stretching your shoulders farther behind your neck. Relax for five seconds.

Repeat five times.

(4) *Pectoral stretch* (fig. 5). Stand sideways to wall, with your palm against wall slightly above shoulder height. Contract by pushing your palm against the wall, and then relax. Rotate your body away from the wall as far as possible while maintaining hand position, hold for five seconds and relax. Repeat in opposite direction.

Repeat five times.

(5) *Trunk rotators* (fig. 6). With feet apart and hands on your hips, turn around as far as possible while maintaining foot position. Hold for five seconds and then repeat in opposite direction. Relax for five seconds.

Repeat five times.

(6) *Neck muscles* (fig. 7). With feet apart, tilt your head sideways forcing your ear as close to your shoulder as possible. Hold for five seconds and repeat on opposite side. Then force your head forwards so that your chin approaches your chest, and hold for five seconds.

Repeat exercise five times.

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We thank Dr W. Andrew C. Scott, M.B., B.S., F.F.A C.S. for his help with statistical analysis, and Miss Marguerite Kelly for secretarial help.

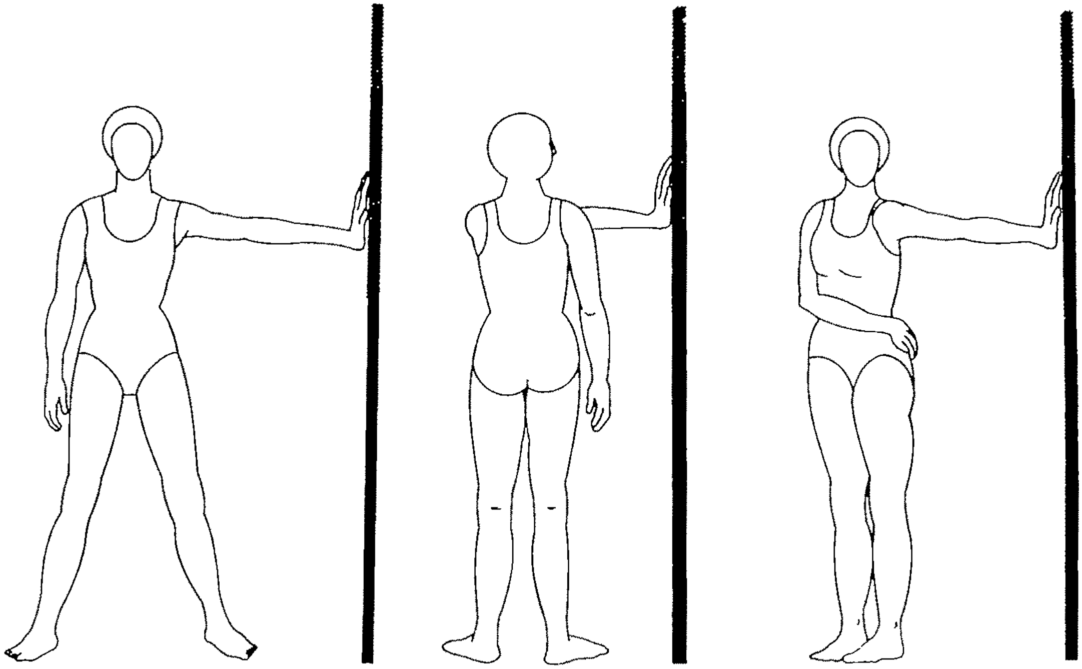

FIG. 5. Pectoral stretch.

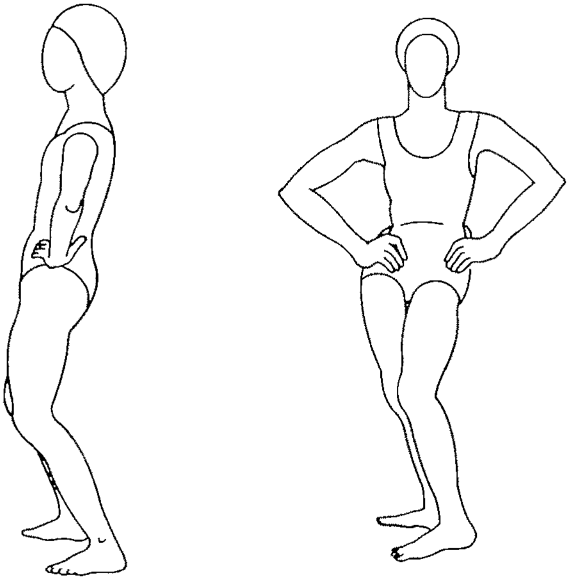

FIG. 6. Trunk rotators.

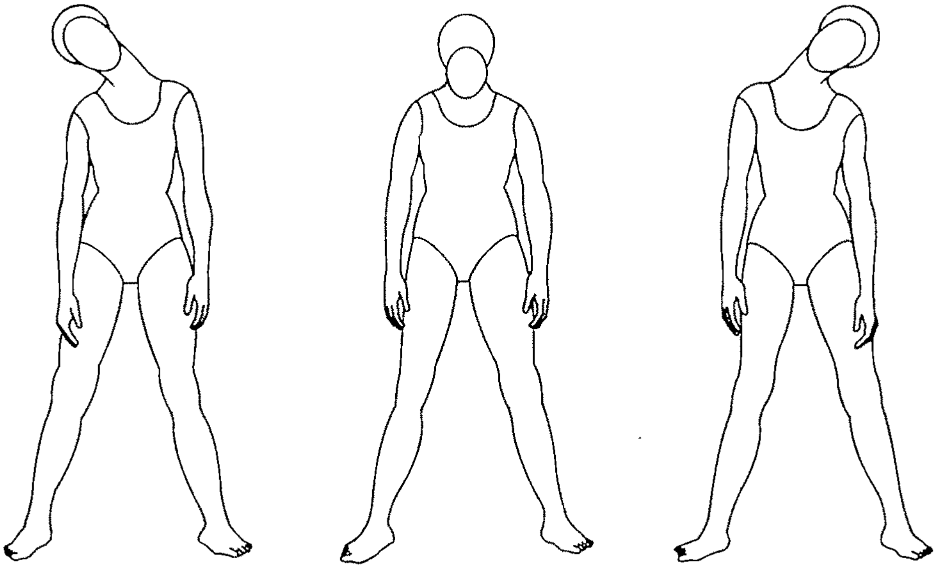

FIG. 7. Neck muscles.

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EFFECT OF SALBUTAMOL AND SUXAMETHONIUM ON THE PLASMA POTASSIUM CONCENTRATION

R. M. SLATER AND I. D. McLAREN

SUMMARY

In a double-blind randomized study, patients received premedication with lorazepam 0.04 mg kg^{-1} and salbutamol 0.1 mg kg^{-1} or lorazepam 0.04 mg kg^{-1} and placebo given orally 2.5–3 h before anaesthesia. The plasma potassium concentration was measured at the time of premedication, before the induction of anaesthesia and at selected intervals after suxamethonium 1 mg kg^{-1} i.v. The plasma potassium concentration was lower in those patients who received salbutamol than in those given placebo, and remained lower at all the subsequent sample times. Oral salbutamol did not appear to affect the incidence of suxamethonium related muscle pain.

Suxamethonium given i.v. may lead to an increase, (0.3–0.5 mmol litre^{-1}) in plasma potassium concentration (Paton, 1956). Weintraub, Heisterkamp and Cooperman (1969) noted that the hyperkalaemia immediately followed the injection of the depolarizing neuromuscular blocker, and reached its peak between 1 and 7 min after the i.v. injection. After denervation injuries or severe burns, the increase in plasma potassium concentration may be of sufficient magnitude to threaten life (Allan, Cullen and Gillies, 1961; Belin and Karleen, 1966; Tolmie and Joyce, 1967).

Extracellular potassium concentrations may be influenced by the state of the adrenergic nervous system. Stimulation of the beta-2 adrenoceptor results in a decrease in extracellular potassium concentration (Smith and Thompson, 1977; Hurlbert, Edelman and David, 1981). Beta-adrenoceptor blockade, on the other hand, has been shown to augment and prolong the increase in potassium concentration after acute potassium loading (Carlsson and Fellenius, 1978). Salbutamol, a beta-2 adrenoceptor stimulant, has been used successfully to alleviate hyperkalaemic attacks in patients suffering from hyperkalaemic familial periodic paralysis (Wang and Clausen, 1976). It was noted that salbutamol also abolished the symptoms of myalgia and weakness in these patients. The present study has been designed to examine the hypothesis that pretreatment with salbutamol might reduce both the increase in potassium concentration and the myalgia often associated with the administration of suxamethonium.

PATIENTS AND METHODS

Forty patients (ASA I or II, aged 16–65 yr) gave written consent to participation in the study which had been approved by the Hospital Ethical Committee. Patients taking beta-adrenoceptor agonists or antagonists, digoxin, calcium antagonists or potassium supplements were excluded from the study. Patients were to undergo minor ENT or dental procedures for which intubation of the trachea would be required.

Immediately before premedication, 10 ml of venous blood was taken from each patient (for the measurement of plasma potassium concentration) via a 21-gauge cannula sited in a vein in the antecubital fossa. The same cannula was used for all sampling and drug administration, and was flushed with saline after use.

Patients were allocated to one of two groups using a randomized, double-blind design. Patients in group A were given salbutamol 0.1 mg kg^{-1} and lorazepam 0.04 mg kg^{-1} by mouth, and those in group B received lorazepam 0.04 mg kg^{-1} and

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TABLE I. *Demographic data*

Group	Sex (M : F)	Age (yr) (Mean (SD) range)	Weight (kg) (Mean (SD) range)
Salbutamol (n = 19)	10 : 9	39 (15) 17–60	67 (9) 60–90
Placebo (n = 21)	9 : 12	36 (14) 18–65	70 (11.5) 55–100

placebo tablets, 2.5–3 h before induction. Heart rate and arterial pressure were recorded at this time and again immediately before the induction of anaesthesia with thiopentone 4–6 mg kg^{-1}. Suxamethonium 1 mg kg^{-1} was administered i.v., the presence or absence of fasciculation noted and the trachea intubated. Blood samples were taken at the time of premedication, immediately before the induction of anaesthesia and at 1, 3, 5, 7, 15 and, where possible, 20 min after the suxamethonium. Anaesthesia was maintained using a spontaneous breathing technique with 66% nitrous oxide and 2–5% enflurane in oxygen via a Magill system. Arterial pressure and heart rate were recorded at intervals throughout the procedure using an automatic device (Dinamap) and the ECG was monitored throughout. During the sampling period, no i.v. fluids were given. The 10-ml aliquots of blood were taken without a tourniquet over 1 min and centrifuged within 5 min of collection. Potassium concentration was measured using a Corning 435 Flame Photometer. A Corning 800 automatic dilutor was used to dilute 0.1 ml of the plasma or standard using lithium 15 mmol $litre^{-1}$ in deionized water. Data represent the means of two readings on each of two aliquots of blood. No haemolysis was noted in any sample.

The patients were given questionnaires to be completed 24 and 48 h after surgery. These contained four main questions with subheadings, all related to postoperative problems. The only question relevant to the study asked, "Since your operation have you noticed any aches or pains in your muscles? If so, please specify whereabouts."

Results were analysed using the Student's *t* test, Chi-squared test and by a two-way analysis of variance.

RESULTS

Nineteen patients received salbutamol and 21 received placebo. The characteristics of the two groups were similar (table I). One patient who had received salbutamol vomited during the injection of thiopentone and was withdrawn from the study. The time from injection to intubation and quality of relaxation for intubation, as assessed by one of the authors (I.D.McL.), was similar in both groups. One patient in the placebo group developed prolonged apnoea (over 3 h) after suxamethonium and was subsequently found to be homozygous for atypical cholinesterase with a dibucaine number of 17.

There were no significant differences in the mean plasma potassium concentrations at the time of premedication (baseline value) (table II). The plasma potassium concentration in the salbutamol group was reduced immediately before the administration of suxamethonium, in relation to both the baseline value and the pre-suxamethonium value in the placebo group ($P < 0.001$). At 1, 3, 5, 7 and 15 min after the administration of suxamethonium, the plasma potassium concentration was significantly lower in the salbutamol group ($P < 0.001$ in all cases). Blood samples were taken 20 min after induction in six patients in the placebo group and nine patients in the salbutamol group. The difference between the values obtained in the two groups was significant ($P < 0.001$) (fig. 1). In the placebo group, the change in plasma potassium concentration was $+0.367 \pm 0.063$ mmol $litre^{-1}$, whereas the change in the salbutamol group was -0.257 ± 0.064 mmol $litre^{-1}$. The maximum re-

TABLE II. *Baseline plasma potassium concentration and mean changes (±SEM) before and after suxamethonium*

Group	Baseline	Before suxamethonium	Time after suxamethonium (min) 1	3	5	7	15	20
Placebo	3.89 (0.055)	−0.02 (0.057)	+0.02 (0.063)	+0.03 (0.07)	+0.11 (0.08)	+0.13 (0.063)	+0.29 (0.065)	+0.33 (0.082)
Salbutamol	3.97 (0.056)	−0.62 (0.069)	−0.45 (0.069)	−0.55 (0.07)	−0.58 (0.076)	−0.48 (0.085)	−0.36 (0.078)	−0.30 (0.10)

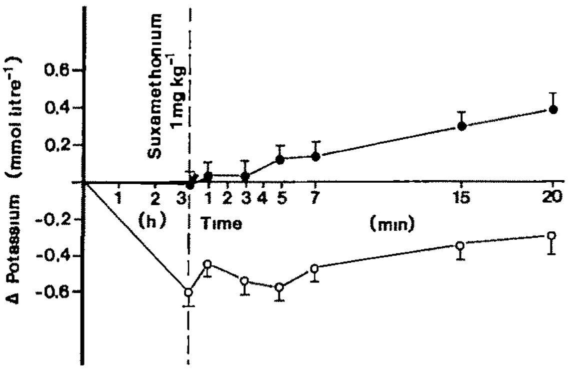

FIG. 1. Change in plasma potassium concentration (±SEM) from baseline and following suxamethonium. ● = Placebo group; ○ = salbutamol group.

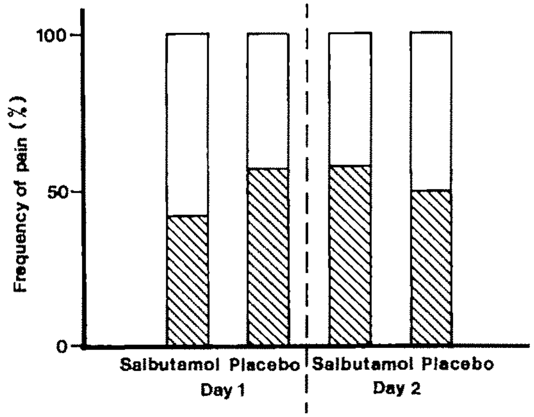

FIG. 2. Frequency of muscle pain following suxamethonium 24 and 48 h after surgery in patients pretreated with salbutamol or placebo. ■ = Pain; □ = no pain.

corded increase in the placebo group was $+0.8$ mmol litre^{-1} and in the salbutamol group $+0.1$ mmol litre^{-1}. However, measured from the time of injection of suxamethonium the increase in potassium concentration in the two groups was similar at all times.

The mean heart rate was increased from baseline both before and 5 min after induction in both groups. However, there was a significantly greater increase in these variables in the salbutamol group before induction. The maximum recorded increase in rate in the placebo group was $+18 \pm 3$ beat min^{-1} and in the salbutamol group was $+32 \pm 4$ beat min^{-1}. There were no significant differences in arterial pressure in either group. Fasciculations were noted in all but three patients; there was no difference between the groups.

All patients were ambulant within 12 h of their operation. Twelve patients in the salbutamol group and 14 in the placebo group returned the questionnaires. The overall frequency of pain was 54% after 24 h and 53% after 48 h, and was similar in both groups (fig. 2).

DISCUSSION

The increase in plasma potassium concentration associated with the administration of suxamethonium is thought to be related to the depolarization of excitable membranes with consequent loss of potassium from skeletal muscle. While this effect is generally small, it becomes significant when there has been muscle injury or when the preoperative plasma potassium concentration is increased (Weintraub, Heisterkamp and Cooperman, 1969). It has been shown, in animals, that the increase in plasma potassium concentration induced by suxamethonium is further increased in the presence of propranolol-induced beta-adrenoceptor blockade (McCammon and Stoelting, 1984). In the present study, salbutamol given in approximately twice the normal oral dose produced a consistent decrease in plasma potassium concentration. The mechanism for this hypokalaemic response seems to be a cellular shift mediated via beta-2 receptors linked to membrane sodium–potassium ATPase, which causes an influx of potassium to the cell (Smith and Kendall, 1984). Salbutamol did not, however, appear to prevent the release of potassium after the administration of suxamethonium. However, the peak potassium concentrations following salbutamol and suxamethonium were lower than those which followed the injection of suxamethonium alone.

Peak plasma concentrations of salbutamol are seen 2.5–3 h after an oral dose. A similar time scale is seen after inhalation of the drug, although changes in FEV_1 occur before the maximum blood concentrations are achieved. Salbutamol given orally undergoes extensive metabolism on first pass through the liver and, at peak plasma concentration, the ratio of salbutamol to its metabolite is 1:4 (Walker et al., 1972). An i.v. infusion of salbutamol 10 µg min^{-1} in human volunteers produced a reduction in plasma potassium concentration of 0.8 mmol litre^{-1} in 1 h (Leitch et al., 1976).

The increase in potassium concentration following suxamethonium can be reduced by pretreatment with a small dose of tubocurarine

(Weintraub, Heisterkamp and Cooperman, 1969). Other methods which may be used to reduce increased potassium concentrations are, however, often associated with marked side-effects such as the potential for hypoglycaemia with insulin and dextrose regimens and the alkalosis and sodium loading with i.v. bicarbonate. Beta-2 stimulation, apart from providing potentially beneficial bronchodilatation, may also produce unwanted effects which include tremor, tachycardia and metabolic effects—such as an increase in circulating glucose and insulin concentrations. In the present study, no patient complained of tremor, but the heart rate was increased significantly. Salbutamol given orally did not alter the incidence of related myalgia.

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EFFECT OF PRE-TREATMENT WITH LYSINE ACETYL SALICYLATE ON SUXAMETHONIUM-INDUCED MYALGIA

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SUMMARY

The hypothesis that prostaglandin inhibitors might reduce the incidence and severity of suxamethonium-induced myalgia was investigated using lysine acetyl salicylate (LAS) 13 mg kg^{-1} i.v. 3 min before the administration of suxamethonium in 20 patients. A comparison was made with atracurium 0.09 mg kg^{-1} (and placebo) in a double-blind prospective randomized trial. LAS and atracurium were effective in reducing the incidence and severity of post-suxamethonium myalgia and the increases in serum potassium concentration. There were no appreciable changes in serum calcium, sodium, chloride, phosphate, magnesium, creatinine, creatine phosphokinase concentrations or plasmacholinesterase activity. Atracurium caused a delay in the onset of action and a decrease in the intensity of suxamethonium-induced neuromuscular block. It is concluded that LAS pretreatment might have a place in suitable patients in the prevention of suxamethonium-induced myalgia and increases in serum potassium concentration.

Attempts to prevent suxamethonium-induced myalgia and hyperkalaemia have included pretreatment with tubocurarine, gallamine (Miller and Way, 1971), vitamin C (Gupta and Savant, 1971), a small dose of suxamethonium (Baraka, 1977), lignocaine and propanidid (Fry, 1978), dantrolene (Collier, 1979), diazepam (Fahmy, Malek and Lappas, 1979) and calcium gluconate (Shrivastava et al., 1983).

In recent years, the role of prostaglandins in the generation of pain has been established (Olley and Coceani, 1980; Metz, 1981) and we are not aware of any previous studies which have used a prostaglandin synthesis inhibitor, such as salicylate, to modify the side effects of suxamethonium.

A prospective double-blind randomized study was planned, based on the theoretical consideration that pretreatment with lysine acetyl salicylate i.v. might modify suxamethonium-induced myalgia or the associated biochemical changes, or both. For comparison, groups of patients pretreated with atracurium and placebo were included.

PATIENTS AND METHODS

The study was approved by the research committee of the University and informed consent was obtained from each patient.

Fifty adult non-pregnant female patients (ASA physical status I) scheduled for diagnostic dilatation and curettage were studied. Patients with suspected neuromusclar, hepatic or renal disease, salicylate intolerance, abnormal bleeding tendency, a history of peptic ulceration, or who were receiving analgesic medication were excluded from the study. All patients were ambulatory 6–8 h after surgery. No premedication was given.

In the operating theatre, ECG was monitored continuously (Medishield M1 monitor) and arterial pressure was measured every 5 min using an electronic oscillometer (Dinamap).

Patients were randomly allocated to three groups. Patients in group I ($n = 20$), received lysine acetyl salicylate (LAS) 13 mg kg^{-1} i.v. to a maximum dose of 1 g as pretreatment, while patients in group II ($n = 15$) received atracurium 0.09 mg kg^{-1}. Group III (controls; $n = 15$)

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patients received 0.2% sodium chloride 10 ml as a placebo.

A standard anaesthetic technique was used for all patients. After pre-oxygenation, anaesthesia was induced with thiopentone 6 mg kg^{-1} and maintained with 70% nitrous oxide in oxygen via a circle absorber system and anaesthetic face mask (no tracheal intubation) and ventilation was assisted manually when necessary. One minute after the administration of the thiopentone, pretreatment was given followed, 3 min later, by suxamethonium 1 mg kg^{-1} i.v. Neuromuscular activity was assessed by observation of thumb adduction, using a peripheral nerve stimulator (Bard) and applying supramaximal stimuli to the ulnar nerve at the elbow via surface electrodes. Onset time (time from the end of injection of suxamethonium to complete disappearance of train-of-four (TOF) response) was recorded. Stimulation was continued until the reappearance of a visible response to stimulation, and time was recorded—corresponding to the duration of action of suxamethonium.

The duration of any fasciculations was recorded and the intensity was graded from 0 to 3 (0 = no fasciculations; 1 = slight eyelid and facial fluttering; 2 = obvious large muscle twitching; 3 = major movements of limb(s)).

An indwelling venous cannula was used to obtain blood samples from an antecubital vein in the arm contralateral to that used for the administration of drugs. Venous blood was collected (without tourniquet) before induction, 1 min after the injection of thiopentone, 3 min after pretreatment and at 3, 5 and 10 min after the injection of the suxamethonium for determination of plasma cholinesterase activity, and the serum concentrations of potassium, sodium, chloride, calcium, phosphate, magnesium, creatinine, creatine phosphokinase (CPK) and salicylate using a Du Pont Automatic Clinical Analyzer. Plasma cholinesterase activity was measured by the change in absorbance at 600 nm following the reduction of butyrylthiocholine to thiocholine. Salicylate packs were used in the Du Pont discrete clinical analyser to measure quantitatively the salicylate in the serum. Under acidic conditions, ferric nitrate forms a complex with salicylate in the salicylate-2 measuring pack. The absorbance of 510 nm attributable to the complex formed is proportional to salicylate concentration. The salicylate-1 pack provided serum–reagent blank at the same wave-length.

Anaesthesia was deepened with halothane after the blood samples had been collected and sent to the laboratory, coded. Thereafter, patients were positioned for surgery (lithotomy).

Postoperative muscle pain was evaluated in all patients after 24 h by one of the authors, who was unaware of the pretreatment given. Verbal categorical pain intensity score 0–10 was used, with the linear analogue pain scale. The scale was explained to the patient: "zero" corresponded to "no pain" and "10" corresponded to "severe unbearable pain". Pain or stiffness in the shoulders, chest, back or upper abdomen was considered evidence of post-suxamethonium myalgia.

Any intra- and postoperative bleeding was noted. In addition, all patients were observed routinely for evidence of nausea, vomiting and drowsiness or dizziness in the postoperative period.

Statistics

Results are expressed as mean ± SD. Statistical analysis of the data was performed by analysis of variance and Chi-square test or Fisher's exact test for homogeneity, where appropriate. Intensity of fasciculations and pain scores were analysed by Mann–Whitney test. The values were considered to be statistically significant when $P < 0.05$.

RESULTS

There was no significant difference among the groups in regard to age or body weight (table I).

The mean onset times of neuromusclar blockade were 52.9 and 57.4 s in groups I and III, respectively (table II). Only four patients (26%) in group II had complete suppression of the TOF response after suxamethonium and this occurred

TABLE I. *Characteristics of patients*

	Age (yr)	Body weight (kg)
LAS group (Group I) (n = 20)	31.4±8.1	66.5±12.9
Atracurium group (Group II) (n = 15)	28.3±6.5	68±9.9
Control group (Group III) (n = 15)	28.8±8.3	66.7±10.9

TABLE II. *Onset time and duration of neuromuscular (NM) blockade. §Data apply to only four patients who developed complete neuromuscular blockade.* *P < *0.05 compared with LAS group;* †P < *0.05,* ‡P < *0.01 compared with atracurium group*

	Onset time (s)	Duration of NM blockade (s)
LAS group (n = 20)	52.9±15.3	321.4±75.8‡
Atracurium group§	83.7±24.3*	150±54.5
Control group (n = 15)	57.4±16.3	282±77.7†

Table III. *Incidence of fasciculations after suxamethonium (No. and* (%))

	Fasciculations			
	0	1	2	3
LAS group (n = 20)	1 (5)	12 (60)	6 (30)	1 (5)
Atracurium group (n = 20)	14 (93.3)	1 (6.6)	0 (0)	0 (0)
Control group (n = 15)	0 (0)	8 (53.3)	3 (20)	4 (26.6)

after a mean time of 83.7 s, which was significantly ($P < 0.05$) prolonged when compared with group I. The rest of the patients in group II did not become apnoeic.

The mean duration of neuromuscular blockade in the control group was 282 s. Pretreatment with LAS did not produce any significant effect on the duration of suxamethonium blockade. In contrast, pretreatment with atracurium reduced the duration of blockade significantly to a mean of 150 s in the four patients who developed complete suppression of the TOF (table II) when compared with either group I ($P < 0.01$) or group III ($P < 0.05$).

Fasciculations were observed in all patients in group III, nineteen (95%) in group I, and one (6.6%) in group II; the mean durations in these groups were 31±16.2, 16.5±8.3 and 5 s, respectively. Pretreatment with atracurium was associated with a significant reduction in the incidence ($P < 0.001$), intensity ($P < 0.001$) and duration of fasciculations when compared with the other groups (table III). Pretreatment with LAS was associated with a significant reduction in the duration ($P < 0.005$), but not the incidence or the intensity of the fasciculations.

Pre-induction values of plasma cholinesterase activity, and the serum concentrations of sodium, chloride, calcium, phosphorus, magnesium, creatinine and CPK were within the normal range and showed no significant changes after pretreatment or the administration of suxamethonium in all the groups. The mean plasma salicylate concentrations were 4.9±0.8, 4.8±0.6, 4.8±0.6 and 4.8±0.5 mg dl^{-1} after 3, 6, 11 and 21 min of LAS administration, respectively.

Induction of anaesthesia with thiopentone resulted, as expected, in a slight reduction in the mean serum potassium concentration in all groups. Pretreatment resulted in a further reduction in the mean serum potassium concentration which was significant in group II ($P < 0.01$).

Administration of suxamethonium 1 mg kg^{-1} resulted in insignificant increases in serum potassium concentrations. The maximum increases occurred in all the groups at 10 min except in group III, where the values were slightly higher at 3 min. The values after suxamethonium in groups I and II were less than the pre-induction values. Pretreatment with atracurium resulted in the least increase in serum potassium concentration (table IV). There was no correlation between the incidence of fasciculations and changes in serum potassium concentrations in any of the groups.

TABLE IV. *Changes in serum potassium concentration (mmol litre*$^{-1}$*). Compared with pre-induction value:* * P < *0.05;* ** P < *0.01*

	Before induction	1 min after thiopentone	3 min after pretreatment	After suxamethonium		
				3 min	5 min	10 min
LAS group (n = 20)	3.79±0.3	3.7±0.2	3.58±0.3	3.61±0.3	3.67±0.3	3.77±0.3
Atracurium group (n = 15)	3.9±0.2	3.8±0.1	3.6±0.1**	3.7±0.1**	3.7±0.1*	3.8±0.1
Control group (n = 15)	3.9±0.3	3.8±0.3	3.8±0.3	4.0±0.3	3.9±0.3	3.9±0.3

Eleven patients (73 %) in the control group, five (25 %) in group I and three (20 %) in group II experienced myalgia after operation (table V). The incidence of pain was significantly less in groups I ($P < 0.025$) and II ($P < 0.005$) when compared with the control group. Furthermore, pain scores were significantly less in groups I ($P < 0.01$) and II ($P < 0.005$) when compared with the control group. No significant differences in the incidence of pain or pain score were observed between groups I and II. There was no correlation between the degree of fasciculation and the occurrence of muscle pain.

No patient received any analgesic or narcotic drugs in the postoperative period. Administration of LAS was not associated with bleeding or any side effects and there were no complications such as vomiting or dizziness after operation in any patient.

DISCUSSION

This trial was designed to fulfil the criteria necessary for a study of post-suxamethonium myalgia. The variables have been reduced to the minimum by standardizing the sex, anaesthetic technique, surgical procedure, posture during surgery, omission of premedication, avoidance of tracheal intubation, early ambulation within 6–8 h after surgery and assessment of patients at 24 h after operation.

Although many theories have been proposed to account for post-suxamethonium myalgia (Konig, 1956; Mayrhofer, 1959; Rack and Westbury, 1966; Waters and Mapleson, 1971; Collier, 1978), the role of prostaglandins as a mediator of pain after the administration of suxamethonium has not been considered. Salicylates have been shown to inhibit prostaglandin synthesis (Moncada and Vane, 1979). If the hypothesis that prostaglandin synthesis is associated with suxamethonium-induced fasciculations were true, LAS—which is a water soluble aspirin—might prevent prostaglandin synthesis and post-suxamethonium myalgia when given in adequate dose.

TABLE V. *Incidence of post-suxamethonium myalgia (No. and (%))*

	Verbal categorical pain intensity score			
	0	1–3	4–6	7–10
LAS group	15	2	3	0
($n = 20$)	(75)	(10)	(15)	(0)
Atracurium	12	1	2	0
group ($n = 15$)	(80)	(6.6)	(13.3)	(0)
Control group	4	4	5	2
($n = 15$)	(26.6)	(26.6)	(33.3)	(13.3)

Pretreatment with either LAS or atracurium has been shown to be effective in reducing the incidence and severity of post-suxamethonium myalgia. In contrast, 73 % of the patients in the control group suffered from mild to severe myalgia (table V). It would appear from the results that LAS pretreament could be used effectively in suitable patients to prevent post-suxamethonium myalgia. Although the changes in prostaglandin concentration in serum have not been measured in this study, work is currently under progress for estimating these after LAS pretreatment.

In normal individuals, the administration of suxamethonium is associated with an increase in the serum potassium concentration by approximately 0.5 mmol litre^{-1} (Weintraub, Heisterkamp and Cooperman 1969). This increase may be modified, but not completely abolished, by different forms of pretreatment (Miller and Way, 1971; Magbagbeola, Adadevoh and Durowoju, 1974; Fry, 1978).

On the basis of the findings of this study, LAS and atracurium were effective in preventing the increases in serum potassium concentration after suxamethonium (table IV). Effects of LAS or atracurium on sodium, chloride, phosphate, calcium, magnesium, creatinine and CPK concentrations, and on plasma cholinesterase activity, were minimal and without obvious pattern.

Pretreatment with atracurium was effective in preventing fasciculations, but it was associated with delayed onset and reduced intensity of suxamethonium-induced blockade. These results correlate with the work of Katz and Katz (1966) and Walts and Dillon (1969). The lack of correlation of fasciculations with myalgia is common (Collier, 1980).

It would appear that pretreatment with LAS could be an alternative means of preventing suxamethonium-induced myalgias and increases in serum potassium concentration in suitable patients.

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BETA-ADRENOCEPTOR BLOCKADE, ALPHA-STIMULATION AND CHANGES IN PLASMA POTASSIUM CONCENTRATION AFTER SUXAMETHONIUM ADMINISTRATION IN DOGS†

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SUMMARY

A study involving 20 mongrel dogs tested the hypotheses that beta-adrenoceptor blockade or alpha-adrenoceptor stimulation may potentiate and prolong the increase in plasma potassium concentration after suxamethonium administration, and that the beta effect is beta$_2$-receptor mediated. Propranolol 0.5 mg kg^{-1} altered the time to peak increase in plasma concentration of potassium after suxamethonium, but did not increase peak concentrations. In controls, the maximum change (0.83 mmol litre^{-1}) occurred at 3 min, while in propranolol-treated dogs the peak change (0.96 mmol litre^{-1} occurred at 30 min. Similar results were obtained when metoprolol 0.25 mg kg^{-1} and ICI 118551 0.1 mg kg^{-1} were used, respectively, as selective beta$_1$- and beta$_2$-adrenoceptor blockers. The increases in potassium concentration following suxamethonium in the metoprolol group (0.98 mmol litre^{-1}) and the ICI 118551 group (0.82 mmol litre^{-1}) reached maximum concentrations at 30 min compared with the controls (0.79 mmol litre^{-1}) which achieved a maximum at 3 min. Phenylephrine was infused at 8 µg kg^{-1} min^{-1} to produce alpha stimulation. The infusion alone altered plasma concentrations of potassium, but the haemodynamic changes were such that conclusions as to the effect of alpha-stimulation on release of potassium after suxamethonium could not be reached

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Adrenoceptor activity has been shown to play a role in the extrarenal disposition of potassium. Evidence in animals and man indicates that beta (β)-adrenoceptor blockade (Rosa et al., 1980) or alpha (α)-adrenoceptor stimulation (Williams et al., 1984) prevents potassium from entering cells, whereas the reverse (β-stimulation or α-blockade) promotes cellular reuptake (Williams et al., 1985). The effects appear to be β_2-mediated (Brown, Brown and Murphy, 1983). Serum potassium concentration increases after the administration of suxamethonium and may attain lethal values in association with denervation or burns (Gronert and Theye, 1975). In the presence of either β-blockade or α-stimulation one might, therefore, expect the normal increase in potassium concentration after suxamethonium to be augmented and prolonged. To explore this possibility, we examined in dogs the effect of β-blockade or α-stimulation on the changes in plasma potassium concentrations after the administration of suxamethonium, and further examined the differential role of β_1- and β_2-receptors in this process, using the selective β-adrenoceptor blocking drugs metoprolol (β_1) and ICI 118551 (β_2).

MATERIALS AND METHODS

Institutional approval was given for the study. Mongrel dogs (11.5–25.5 kg) were anaesthetized with thiopentone 20–25 mg kg^{-1} i.v. The trachea

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was intubated and mechanical ventilation instituted. Anaesthesia was maintained with 1% halothane in oxygen. No neuromuscular blockers were administered before the suxamethonium, and there was no clinical evidence of inadequate anaesthesia. Catheters were placed percutaneously in a femoral artery and vein. Systemic arterial pressure was recorded continuously. Ventilation was adjusted to maintain the Pa_{CO_2} at 4.7–6 kPa. Blood-gas tensions were measured throughout the study and ventilation adjusted, as necessary. Once stable anaesthesia was established, an infusion of 0.9% saline 3 ml kg^{-1} was started and maintained throughout each investigation. All drugs except suxamethonium were diluted in saline, and administered via the infusion. All measurements were made from arterial blood samples which were drawn into pre-heparinized syringes, placed on ice and analysed for plasma potassium concentration with an ion-selective electrode (Nova 1) (Ladenson, 1979). The experiment was performed in two parts.

Part 1

The response to suxamethonium 1 mg kg^{-1} was noted during the infusion of physiological saline for each dog. At intervals of at least 6 days, the dogs were re-anaesthetized and the responses to the administration of suxamethonium in the presence of phenylephrine or propranolol recorded.

Controls (n = *8*). The response to suxamethonium was noted during the infusion of saline in each dog. Of these eight dogs, two subsequently received phenylephrine but no propranolol, and two propranolol but no phenylephrine. The other four received on separate occasions either propranolol or phenylephrine. Only the six dogs that received the study drug acted as controls for their group.

Phenylephrine infusion and suxamethonium (n = *6*). Phenylephrine 8 µg kg^{-1} min^{-1} was infused from the start of the saline infusion. This dose was based on previous reports of the hyperkalaemic effect of phenylephrine (Todd and Vick, 1971). Four of these dogs also received (on another occasion) an infusion of phenylephrine 8 µg kg^{-1} min^{-1}, but no suxamethonium.

Propranolol and suxamethonium (n = *6*). Propranolol 0.5 mg kg^{-1} was given over 10 min from the start of the saline infusion, and maintained at 2 µg kg^{-1} min^{-1} thereafter.

In all groups, apart from the group receiving phenylephrine without suxamethonium, suxamethonium 1 mg kg^{-1} was given 30 min after the start of the infusion and blood was analysed for plasma potassium concentration at the following times: pre-infusion, infusion +10, +25 (duplicate samples), and 1, 3, 5, 10, 15, 30, 60 and 90 min after suxamethonium administration. Timing and dosage of drugs are shown in figure 1.

Part 2

A further set of studies was performed to characterize the differential effect of β_1- and β_2-blockers.

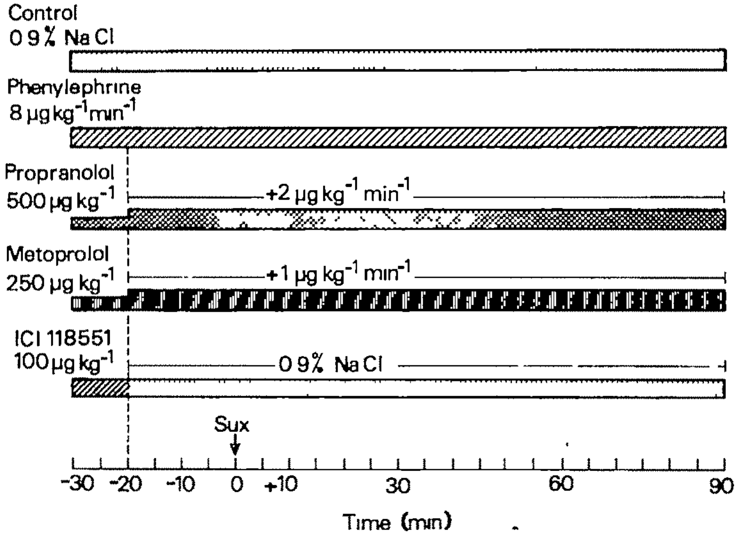

FIG. 1. Timing and doses of drugs administered.

Controls (n = *8*). These consisted of the same eight dogs for which data after saline infusion and suxamethonium were already available from Part 1. These were compared with two separate groups of dogs.

Metoprolol (n = *6*). Metoprolol 0.25 mg kg^{-1} was administered over 10 min, followed by 1 μg kg^{-1} min^{-1}.

ICI 118551 (n = *6*). ICI 118551 0.1 mg kg^{-1} was given over 10 min. This dose was chosen to give adequate β_2-blockade without major β_1 effects in dogs (D. Riley, ICI Pharmaceuticals, England; personal communication).

As with propranolol, both metoprolol and ICI 118551 were started 30 min before the administration of suxamethonium (fig. 1). Blood was drawn for analysis of plasma potassium concentration as for Part 1.

The effectiveness of β_1-blockade was tested in the propranolol and metoprolol groups with a bolus of isoprenaline 0.5 μg kg^{-1} at the conclusion of the study. Since ICI 118551 should have little β_1 effect, the isoprenaline test was not performed in this group.

Statistical analyses

Statistical treatment of the data utilized analysis of variance, with allowance for repeated measures, on plasma potassium concentration and on the change in plasma potassium concentration after suxamethonium. The significance of comparisons of plasma potassium concentration with baseline within a treatment group and comparisons of change in plasma potassium concentration between groups was determined by *t* statistics, setting the critical value according to Bonferroni's inequality (Miller, 1981) so that the simultaneous significance level would not exceed 0.05. Thus, for example, to ensure that a set of five significance tests on the same data has, at most, a 0.05 probability of yielding one or more significant results by chance alone, the significance level for each of the five tests should be 0.05/5 = 0.01.

RESULTS

The suxamethonium-induced changes in plasma potassium concentration from baseline (5 min before administration of suxamethonium) for the β-blocked dogs are shown in tables I and II. There were no significant differences in the baseline values of potassium concentration between the groups. All groups experienced a significant increase in plasma potassium concentration by 3 min after suxamethonium. This increase persisted for 30–60 min. In the control group, the potassium reached maximum concentration at 3 min and remained increased for 30 min before returning to baseline (tables I and II). The β-blocked groups also showed significant increases in potassium concentration at 3 min, but peak potassium concentrations occurred at 30 min. These reverted to baseline only at or after 60 min (tables I and II). There were no statistically significant differences between the maximum

TABLE I. *Changes (SD) from baseline in potassium concentration (mmol litre*$^{-1}$*) after suxamethonium. * Significant changes from baseline within a group* (P < *0.05, simultaneous*)

Time after sux. (min)	Control	Propranolol
1	0.435 (0.141)	0.395 (0.059)
3	0.828 (0.234)*	0.503 (0.091)*
5	0.797 (0.208)*	0.467 (0.223)*
10	0.660 (0.248)*	0.593 (0.321)*
15	0.762 (0.311)*	0.772 (0.310)*
30	0.623 (0.615)*	0.963 (0.375)*
60	0.057 (0.441)	0.268 (0.344)
90	−0.212 (0.150)	0.035 (0.239)

Table II. *Changes (SD) from baseline in potassium concentration (mmol litre*$^{-1}$*) after suxamethonium. Significant changes* (P < *0.05, simultaneous*)*: *from baseline within a group; †from control group*

Time after sux. (min)	Control	Metoprolol	ICI 118551
1	0.408 (0.146)*	0.240 (0.196)	0.237 (0.219)
3	0.790 (0.372)*	0.485 (0.275)*	0.488 (0.237)*
5	0.766 (0.273)*	0.452 (0.251)*	0.462 (0.193)*
10	0.632 (0.226)*	0.500 (0.246)*	0.480 (0.184)*
15	0.702 (0.309)*	0.648 (0.283)*	0.670 (0.211)*
30	0.636 (0.540)*	0.978 (0.488)*	0.815 (0.191)*
60	0.074 (0.393)	0.568 (0.408)*†	0.482 (0.172)*
90	−0.178 (0.204)	0.093 (0.267)	0.077 (0.131)

TABLE III. *Changes (SD) from baseline in potassium concentration (mmol litre^{-1}). Control (sux. only) and phenylephrine with and without suxamethonium*

Time after sux. (min)	Control	Phenylephrine	Phenylephrine without sux.
1	0.442 (0.154)	0.431 (0.419)	—
3	0.732 (0.410)	0.444 (0.460)	—
5	0.750 (0.314)	0.444 (0.481)	0.000 (0.14)
10	0.630 (0.254)	0.536 (0.557)	—
15	0.782 (0.320)	0.621 (0.566)	0.118 (0.091)
30	0.692 (0.439)	0.651 (0.562)	0.272 (0.187)
60	0.078 (0.362)	0.462 (0.467)	0.433 (0.398)
90	−0.128 (0.216)	0.496 (0.651)	0.553 (0.243)

concentrations obtained in each group. The time course of the change in potassium concentration, however, was altered by all of the β-blockers compared with their respective controls ($P < 0.01$). For the metoprolol group, the change in potassium value at 60 min was significantly greater than controls for the same time ($P < 0.05$) (table II). There was no difference between the metoprolol and ICI 118551 groups in the changes in potassium concentration with time. After isoprenaline 0.5 μg kg^{-1}, the average maximum increase in heart rate in propranolol-treated dogs was 6 beat min^{-1} and in the metoprolol group it was 35 beat min^{-1}.

Phenylephrine alone caused an increase in plasma potassium concentration after 10 min which returned to baseline after 25 min. If no suxamethonium was given, the plasma potassium concentration increased slowly subsequently. If suxamethonium was given, there was an immediate increase which was sustained (table III). These changes, however, were measured during a period of marked cardiovascular and metabolic derangements. Average arterial pressure for all dogs receiving phenylephrine (whether given suxamethonium or not) was 130/79 mm Hg before infusion and 278/162 mm Hg at 25 min of infusion. There was an associated metabolic acidosis which became increasingly pronounced over time. In two instances, frank pulmonary oedema necessitated termination of the study.

DISCUSSION

Adrenoceptor agents, probably acting via the Na^+/K^+ pump (Clausen and Flatman, 1977), play a role in the extrarenal disposition of potassium. Adrenaline leads to an increase in the extrarenal uptake of potassium, almost certainly mediated through β_2-adrenoceptor stimulation (Brown, Brown and Murphy, 1983; De Fronzo, Bia and Birkhead, 1981). This conclusion is reinforced by the observation that β_2-stimulation can decrease plasma potassium concentrations arising from the hyperkalaemia secondary to familial periodic paralysis (Wang and Clausen, 1976). Exercise leads to an increase in plasma potassium concentration. This is enhanced by β-blockade, especially when non-selective as opposed to β_1-selective blockade is induced (Carlsson et al., 1978). β-Blockade has also been shown to impair the extrarenal disposition of a potassium load in some patients (Rosa et al., 1980; Torretti et al., 1986), although this has not always been confirmed (Rolf Smith et al., 1984). Chronic β-blockade alone leads to a slight increase in plasma potassium concentration (Lundborg, 1983).

It has also been suggested that α-adrenoceptor stimulation impairs the extrarenal disposition of potassium, and that at least some of the increase in plasma potassium concentration seen in subjects receiving chronic β-blocker therapy may be secondary to the unopposed effects of α-stimulation (Williams et al., 1984). Therefore, we might expect β-blocker or α-stimulation to have some effect on potassium release after suxamethonium. Our study examined this hypothesis and attempted to differentiate the β_1 and β_2 effects using metoprolol (β_1) and ICI 118551 (an experimental selective β_2 antagonist) as selective β-blockers. Our results demonstrate that β-blockade alters the time to peak potassium concentration after suxamethonium, and the duration of the increase, but does not significantly affect the magnitude of the response.

Our data confirm the findings of Todd and Vick (1971) that phenylephrine at an infusion rate of 8 μg kg^{-1} in the dog leads to an initial increase and subsequent reduction in plasma potassium concentration. We used this infusion rate since they concluded that the hyperkalaemic effect of phenylephrine was maximum at this dose. However, these authors failed to comment on the profound cardiovascular effects of this infusion. Arterial pressures were increased to non-physiological values, and profound metabolic acidosis developed, presumably secondary to extreme vasoconstriction and inadequate perfusion. In this situation, it is not possible to determine whether the changes in plasma potassium concentration were caused by the peripheral vascular effects, or by the direct cellular effects of phenylephrine. The same comments apply to the changes in plasma potassium concentration after suxamethonium in the presence of phenylephrine, in that the metabolic consequences of the cardiovascular effect were enough to mask and outweigh any direct effect at the cellular level.

In dogs, an infusion of propranolol alone had no effect on plasma potassium concentration (Todd and Vick, 1971). The dose of propranolol used in our study has been shown to have good blocking activity in the dog, and is similar to doses used by other workers (Harry et al., 1973). The bolus of isoprenaline 0.5 $\mu g\ kg^{-1}$ administered at the end of each investigation confirmed the efficacy of the blockade. We deliberately used a relatively small β_1-blocking dose of metoprolol because of a desire to avoid the β_2 effects seen with larger doses. This is reflected in the results of the isoprenaline challenge test. We found that both non-selective and selective β-blockade altered the time pattern of the release and re-uptake of potassium after suxamethonium. However, the peak concentrations were not increased significantly in the propranolol group. Only for metoprolol at 60 min were individual values significantly different from control. β-Blockade may effect the release of potassium from cells, thus explaining the later peak for the plasma potassium concentrations following suxamethonium (Carlsson et al., 1978). Our results contrast with the findings of McCammon and Stoelting (1984), who described a marked increased in plasma potassium concentration after suxamethonium in dogs given propranolol. The increase in potassium concentration in their propranolol-treated dogs appeared to be greater and more prolonged than ours. The increase in their controls seemed to be less than in our study. We can find no easy explanation for these differences. With the exception of the additional use of nitrous oxide, their anaesthesia was similar to ours. Their dogs received an initial bolus of 0.25 $mg\ kg^{-1}$ of propranolol, with subsequent increments of 0.1 $mg\ kg^{-1}$. Suxamethonium was administered 10 min after the β-blocker. We cannot comment on their method of collecting, storing and evaluating potassium concentrations since this was not discussed; however, these factors could well affect the results (Hill et al., 1980).

Although β_2-blockade, compared with β_1, selectively impairs extrarenal uptake of potassium, we found no difference between the predominantly β_1 effect of metroprolol and the β_2 action of ICI 118551 following suxamethonium. Metoprolol also has some β_2 activity, and it is possible that the doses we used were sufficient to unmask this effect. The dose of ICI 118551 was chosen as adequate for a β_2-block without significant β_1 effects.

We are aware of no case reports in man implicating β-receptor blockade leading to hyperkalaemia following suxamethonium. It is reasonable to expect such blockade to have some effect on the release of potassium after suxamethonium. However, if these data can be extrapolated to man, it appears that lethal hyperkalaemia probably would not result from the use of suxamethonium in the presence of acute β-blockade.

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INVOLVEMENT OF NUCLEOPHILES IN THE INACTIVATION OF ATRACURIUM

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SUMMARY

Atracurium was incubated in 0.9% sodium chloride solution at pH 7.4 and 37 °C. The following compounds were added to the incubation solution: propionic acid, alanine and cysteine (0.1 mol litre^{-1} final concentration). Metocurine was also incubated with cysteine under identical conditions. Aliquots of the incubation solutions were injected i.v. to anaesthetized rats at the start (0 min) and at the end of incubation (45 min), and the indirectly elicited, single twitches of the gastrocnemius muscle were observed. Whereas inactivation of atracurium proceeded slowly in the control solution and in the presence of sodium propionate, the presence of alanine and, especially, of cysteine markedly enhanced the inactivation. Incubation of metocurine with cysteine did not alter the pharmacological responses. The concentration of cysteine decreased progressively during its incubation with atracurium (37 °C, pH 7.4). We conclude that the data are compatible with the postulate that a nucleophile may enhance the degradation of atracurium by a reaction with the parent compound (nucleophilic substitution reaction), by reaction with acrylates (Michael addition) or both.

Studies that demonstrated the generation of laudanosine *in vitro* (Stiller, Cook and Chakravorty, 1985) and *in vivo* (Fahey et al., 1985) do not prove that the degradation of atracurium proceeds solely by Hofmann elimination. Laudanosine may be formed from atracurium either by an elimination reaction—as originally postulated by Stenlake and colleagues (1981)—or by a nucleophilic substitution reaction. The latter (Hendrickson, Cram and Hammond, 1970) results from a nucleophilic attack on the beta-carbonyl atom vicinal to a quaternary nitrogen. In the case of atracurium, the end-products would be laudanosine and the residue of the parent drug covalently bound to the nucleophile. Hence, both the inactivation of atracurium and the generation of laudanosine can ensue from either the elimination or the substitution reactions. We elected to test the hypothesis that nucleophiles enhance the inactivation of atracurium *in vitro*.

A nucleophilic substitution reaction may be suspected if, at the same pH and temperature, the inactivation of atracurium proceeds faster with a nucleophile in the incubation solution than without it. We selected cysteine as the test nucleophile. A second neuromuscular blocking drug, metocurine, was included in the study to test for any non-specific effects of cysteine on the paralysis of the skeletal muscle produced by non-depolarizing neuromuscular blockers. Metocurine shows chemical similarities to atracurium (Bowman, 1983). However, in contrast to atracurium, its duration of action is limited by redistribution and elimination rather than by biotransformation (Miller and Savarese, 1986).

MATERIALS AND METHODS

All incubations were carried out in 0.9% sodium chloride solution (final volume 10 ml) at 37 °C. When required, L-cysteine, L-alanine or propionic acid were added (final concentration 0.1 mol litre^{-1}). Before the addition of cysteine, and continuously afterwards, the solution was deoxygenated by purging it with humidified nitrogen gas at 37 °C. Commercial preparations of atracurium or metocurine were then added (initial

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concentrations were 1 mg ml^{-1} and 0.02 mg ml^{-1}, respectively). All solutions were adjusted to pH 7.4 ± 0.05 (at 37 °C) with 0.1 mol $litre^{-1}$ or 0.01 mol $litre^{-1}$ of either sodium hydroxide or hydrochloric acid before the addition of the neuromuscular blocker as well as during the 45 min of incubation. The acidity was continously monitored with a glass pH electrode (Ross Series Micro Combination Electrode No. 811500, Orion Research, Inc., Cambridge MA) connected to a digital pH meter.

Aliquots of the incubation solutions were administered i.v. to male rats (210–290 g, Wistar strain). The animals were anaesthetized with sodium pentobarbitone 65 mg kg^{-1} i.p. and their lungs ventilated mechanically. They were prepared as described previously (Nigrovic et al., 1985). Briefly, cannulae were inserted to the femoral artery and vein to permit the measurement of arterial pressure and the administration of drugs, respectively. A solution of 0.9 % sodium chloride was infused at 6 ml kg^{-1} h^{-1} through the venous cannula. The gastrocnemius muscle of the opposite extremity was prepared for the monitoring of twitch height by attaching its severed end to a force transducer (Grass FT.03). The sciatic nerve supplying the test muscle was transected and its distal stump placed over a pair of platinum stimulating electrodes. Single supramaximal square wave stimuli were applied at 0.2 Hz (duration 0.2 ms). After optimization of the preload, and before the administration of the myoneural blockers, the mechanical twitches produced 40-mm pen deflections as recorded on the polygraph. At the start of incubation, aliquots of the incubation solution were injected i.v., delivering atracurium 2.4 mg kg^{-1} or metocurine 0.025 mg kg^{-1}. Identical volumes were injected at the end of the 45-min incubation period. Because of the fast recovery of the muscle twitch after the administration of atracurium (Nigrovic et al., 1985), the second injection was administered to the same animal. The second injection of metocurine was administered to a different animal in order to avoid a cumulative effect. Incubation and the bioassay of atracurium were repeated four times for each additive to the incubation solution. Tests with metocurine were performed in duplicate. At the termination of the *in vivo* experiments, arterial blood samples were collected for the determination of pH and the partial pressure of carbon dioxide.

Twitch height obtained after the administration of the neuromuscular blocker was expressed as percent of the respective preinjection height. The following variables were derived from the twitch recordings: (1) onset time (the time (s) from the injection to the maximal twitch inhibition); (2) the magnitude of the maximal neuromuscular block (100 % minus twitch height (%)); (3) duration of paralysis (time (s) from the administration to 10 % recovery); and (4) the rate of recovery (percent of the twitch height recovered per minute). Data were analysed using analysis of variance and are presented as mean ± SEM.

In an additional series of investigations, various concentrations of atracurium were incubated with cysteine 10^{-3} mol $litre^{-1}$ in 0.9 % sodium chloride. Measures to minimize the formation of cysteine during the incubation at pH 7.4 and 37 °C were identical to those in earlier studies. The total incubation volume was 10 ml. Sodium hydroxide was used to maintain pH at 7.4 (< 100 μl). At predetermined time intervals, aliquots of the incubation mixtures were analysed spectrophotometrically for the mercapto groups of cysteine (Ellman, 1959). All data were expressed in percent of the initial concentration of cysteine (determined immediately after the addition of atracurium).

RESULTS

Aliquots of each incubation solution were injected i.v. to rats within 2 min of the addition of atracurium. Independent of the additives present in the incubation solutions, these injections rapidly (within 30–40 s) produced a complete skeletal muscle paralysis which lasted for 200–300 s (table I). The paralysis was followed by rapid recovery. Aliquots of the incubation solutions collected and injected after 45 min of incubation produced a characteristic pattern of pharmacological responses. The pattern was dependent on the additives to the incubation solutions. An almost complete neuromuscular blockade ensued following injections of control samples (no additives) and of those containing sodium propionate. The onset of blockade, however, was slower and its duration shorter when compared with the corresponding values produced by the first injection of the same solutions. When atracurium was incubated with alanine, the injection of aliquots at the end of the incubation period resulted in a barely discernible diminution of blockade ($P = 0.025$ for comparisons with the control samples and the samples containing

TABLE I. *The effect of propionic acid and its derivatives on the* in vitro *inactivation of atracurium. Incubation was carried out in 0.9% sodium chloride solution (pH 7.4 and 37 °C). The dose of atracurium at 0 min of incubation was 2.4 mg kg⁻¹ i.v. Data are presented as mean ± SEM (see Materials and Methods for further details).* [a]*Complete neuromuscular blockade was achieved in all four animals.* [b]*Three rats showed no response to the injection of an aliquot collected at the end of 45 min of incubation. In the fourth rat the twitch was reduced by 11%. These results are reported without a statistical summary.* [c]*The absence of neuromuscular blockade precluded the calculation of these variables.* [d]*Arterial blood samples were collected after complete recovery from the second injection*

Added to the incubation solution	Duration of incubation (min)	Onset of maximal blockade (s)	Duration of blockade (s)	Magnitude of blockade (%)	Recovery rate (% min^{-1})	Arterial blood[d]	
						pH	P_{CO_2} (kPa)
Nil	0	29.6±5.1	294±7	100[a]	32.2±3.1	7.37±0.02	4.0±0.4
	45	47.6±6.5	202±32	99.7±0.3	35.7±2.2		
Sodium propionate 0.1 mol litre^{-1}	0	39.1±11.3	273±46	100[a]	47.5±5.6	7.34±0.11	4.3±0.9
	45	50.7±5.4	220±34	99.5±0.3	45.6±5.7		
Alanine 0.1 mol litre^{-1}	0	40.0±10.0	251±20	100[a]	36.5±7.2	7.30±0.06	4.4±0.1
	45	61.3±5.1	120±15	96.0±0.6	44.4±4.2		
Cysteine 0.1 mol litre^{-1}	0	42.8±9.9	215±16	99.7±0.3	53.1±0.9	7.40±0 04	4.1±0.5
	45	c	c	0, 0, 0, 11[b]	c		

TABLE II. *Disappearance of cysteine during incubation with atracurium (37 °C, pH 7.4):* n = 5 *for each concentration of atracurium. Data represent mean ± SEM.* [a]*Concentrations of cysteine were below detectable concentrations*

Molar concentration (10^{-3} mol litre^{-1})		Percent cysteine remaining after incubation for				
Cyst.	Atrac.	0 min	15 min	30 min	45 min	60 min
1	0	100	97.2±2.6	96.5±3.5	97.4±3.7	102.0±5.3
1	1	100	96.7±4.2	82.2±1.3	73.6±3.9	58.7±4.6
1	4	100	46.0±5.8	9.1±3.5	1.2±0.8	a
1	8	100	6.2±1.9	a	a	a

sodium propionate). In addition, the onset of blockade was markedly delayed and its duration was shortened. When cysteine was present in the incubation solution, injection of the aliquots at the end of incubation did not cause any decrease of the twitch height in three rats and only an 11% decrease in the fourth. The absence of pharmacological responses precluded calculation of the other variables and, moreover, made any statistical analysis inappropriate and unnecessary. The lack of any changes clearly indicates that atracurium was no longer present in the incubation solutions containing cysteine.

Data on pH and on the partial pressure of carbon dioxide in arterial blood samples collected at the end of the *in vivo* studies revealed no differences among the four groups.

In a smaller, separate series, the influences of cysteine (whether present or not) and of the duration of incubation (0 or 45 min) on the pharmacological profile of metocurine were tested in a 2×2 experimental design (with two rats in each group). Neither the presence of cysteine nor the duration of incubation exerted any influence on the paralysis produced by metocurine (pooled results for all four groups: onset of paralysis (90.0±14.5) s, duration of paralysis (371±123) s, magnitude of neuromuscular blockade (98.7±1.6)%, and rate of recovery (8.6±2.03)% min^{-1}).

Incubation of cysteine with atracurium (table II) led to a disappearance of cysteine. The amount of cysteine lost during the incubation with atracurium was time-dependent and the rate of its disappearance was directly related to the concentration of atracurium.

DISCUSSION

Our data indicate that the incubation of atracurium with cysteine leads to rapid inactivation of the atracurium (table I), and that cysteine is consumed during the incubation (table II). Both observations are compatible with the notion that cysteine interacts either directly with atracurium or with one of its metabolities. One example of each possibility will be given and analysed.

The reverse ester structure of atracurium (Stenlake et al., 1981) endows the molecule with the propensity to interact with nucleophiles. Two pathways, the elimination (Hofmann) reaction and the nucleophilic substitution reaction, are possible. In the elimination reaction, an anionic nucleophile—for example a hydroxyl group—removes one hydrogen (as a proton) from the alpha-carbonyl carbon. This leads to the breakdown of atracurium and the formation of one molecule of water, laudanosine, and an acrylate. As a result of their electrophilic character, acrylates avidly react with sulphydryl nucleophiles (Michael addition). For example, ethyl acrylate was shown to react with glutathione or with non-protein sulphydryl groups *in vitro* (Miller et al., 1981). *In vivo*, acrylates are excreted in urine as derivatives of mercapturic acid, again implying an antecedent reaction with glutathione (Delbressine, Seuter-Berlage and Seuter, 1981). In our investigations, Michael addition would lead to the disappearance of both acrylates and cysteine and the generation of a thio-ether adduct. Since acrylates are a product of Hofmann elimination, their removal from the incubation solution would be followed by enhanced degradation of atracurium via the elimination reaction.

The second possible interpretation of our data is a direct reaction between cysteine and atracurium in a nucleophilic substitution reaction. In this reaction the nucleophilic sulphydryl group of cysteine attacks the beta-carbonyl carbon in the chain of atracurium. The reaction also leads to inactivation of atracurium and the consumption of cysteine. The products are laudanosine and an adduct of cysteine with the atracurium residue. This adduct is chemically identical to the thio-ether adduct formed by cysteine and the acrylate residue of atracurium.

Our results suggest the following proposals pertaining to the degradation of atracurium in the nucleophile-rich environment *in vivo*: (1) Nucleophiles enhance the degradation of atracurium. (2) Laudanosine can be generated, not only by the elimination, but also by the nucleophilic substitution reaction. (3) After the cleavage of laudanosine, the residual portion of the atracurium molecule may form a thio-ether adduct with a nucleophile. The adduct may be formed either directly in a reaction of the nucleophile with atracurium or by Michael addition of the nucleophile to the acrylate residue. (4) Since the "quaternary acid" metabolite of atracurium has the reversed ester structure converted to an anionic carboxylic group, the "quaternary acid" is not likely to react with an endogenous nucleophile via either the elimination or the nucleophilic substitution reaction.

The *in vivo* fate of the two bulky end-groups in atracurium appears reasonably well defined. As they are cleaved from atracurium, each moiety is converted to a tertiary amine, laudanosine. On the other hand, there is little or no information about the *in vivo* fate of the aliphatic chain that initially connected the two bulky ends in the parent molecule. On the basis of the above interpretation of our data, one may postulate that this portion of the atracurium molecule binds to endogenous nucleophiles. If the binding occurs to glutathione, this part of the parent drug would be excreted in urine as a derivative of mercapturic acid. It is important to contrast these degradation pathways of atracurium with yet another pathway, namely the hydrolysis of the ester bonds. Hydrolysis of atracurium destroys its ester character. Hence, complete hydrolytic degradation would preclude the interaction of atracurium with endogenous nucleophiles. Thus, the overall fate of atracurium *in vivo* will depend on the extent of ester hydrolysis.

In summary, our data suggest an additional inactivation pathway for atracurium *in vivo* and indicate that the parent molecule or one of its degradation products, or both, may react with endogenous nucleophiles.

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COMPARATIVE NEUROMUSCULAR BLOCKING EFFECTS OF VECURONIUM, PANCURONIUM, ORG 6368 AND SUXAMETHONIUM IN THE ANAESTHETIZED DOMESTIC PIG

A. W. MUIR AND R. J. MARSHALL

SUMMARY

The neuromuscular blocking and cardiovascular effects of three competitive neuromuscular blocking drugs, vecuronium, pancuronium and Org 6368, and the depolarizing drug suxamethonium, have been evaluated in the anaesthetized domestic pig. Both the relative time-course and the order of potency of the drugs agreed well with published data in man. In addition, the cardiovascular side-effects of pancuronium and Org 6368 were identified readily. These preliminary results suggest that the pig may provide more reliable neuromuscular blocking time-course data than does the more commonly utilized cat model.

There have been numerous attempts to develop a competitive neuromuscular blocking agent which would replace suxamethonium as an agent with which to facilitate tracheal intubation. This goal, first identified by Foldes (1957) has so far remained elusive, although many possible contenders have been identified in anaesthetized animals (Hughes, 1984). Although testing in the anaesthetized cat has played a major role in the identification and selection of such contenders for clinical trial, the cat model, although predicting neuromuscular blocking potency and cardiovascular side-effects accurately, has proved of little value in predicting duration of action in man. This is true for dipyrandium (Mushin and Mapleson, 1964), NN^1-dimethyl-conessine (Busfield et al., 1968), fazadinium (Hughes, Payne and Sugai, 1976), dacuronium (Norman and Katz, 1971) and for the 17-desacetoxy analogue of pancuronium, Org 6368 (Baird, 1974), all of which were found to be significantly longer-acting in man than in the cat. Indeed, it is now generally held that monkeys (rhesus, macaca or cynamolgus) provide the best predictive profile of the duration of action of neuromuscular blockers in man (Brittain and Tyers, 1973; Hughes, 1984). However, for both economic and ethical reasons, screening of new neuromuscular blocking agents in primates is not a practical proposition. The aim of this study was to investigate whether the anaesthetized domestic pig furnished more predictable data on non-depolarizing neuromuscular blocking agents for man than does the more commonly used anaesthetized cat.

MATERIALS AND METHODS

Domestic pigs (Landrace–Welsh cross) of either sex (10.4–15.1 kg) were given a tranquillizing dose (approximately 2 mg kg^{-1}) of azaperone (Suicalm, Janssen) about 20 min before the induction of anaesthesia with 3–4% halothane in oxygen. Following induction, anaesthesia was maintained with α-chloralose 200 mg kg^{-1} (2 ml kg^{-1} of α-chloralose 100 mg ml^{-1} in polyethylene glycol 300) given slowly into the jugular vein. Approximately 1 h later, anaesthesia was supplemented with additional chloralose given by a slow i.v. infusion (33 mg kg^{-1} h^{-1}) which was continued throughout the investigation. The lungs were ventilated artificially with room air via a tracheal cannula at a rate of 28 b.p.m. and a tidal volume of 12–14 ml kg^{-1}. Arterial $P\text{CO}_2$ was maintained between 4.26 and 5.32 kPa.

Arterial pressure was recorded through a polythene catheter placed in the right carotid artery and connected to a Gould–Statham pres-

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sure transducer. Heart rate was monitored continuously by using the arterial pulse pressure to trigger a Grass 7P4F cardiotachometer or Devices instantaneous heart rate meter. Drugs were administered through a catheter introduced to the remaining jugular vein.

The tibialis anterior and soleus muscles were dissected free from surrounding tissue and attached to force displacement transducers (Grass FT10 or FT03) with strong linen threads. A resting tension of 30 g was applied to each muscle. In the same leg, the left sciatic nerve was exposed in the popliteal space and crushed centrally. Twitches were evoked every 10 s by stimulating the two branches of the sciatic nerve supplying the lower leg—immediately distal to the point where the nerve divides—using square wave pulses of 0.25 ms duration and at twice the voltage to produce maximum contractions.

Dose–inhibition plots for the neuromuscular blocking compounds on the responses of the two muscles to sciatic nerve stimulation were constructed by injecting increasing doses of drug. Doses of drug were administered at least 1 h apart (1 h after 90% recovery of twitch height). In individual animals the dose of drug producing 90% depression of tibialis twitch tension (ED_{90} dose) was estimated using linear interpolation of the dose–inhibition line for that muscle. A dose, equivalent to three times the calculated ED_{90}, was injected towards the end of each investigation to evaluate the effects of clinically relevant higher doses in this model.

Dose–inhibition lines from composite data for each compound were plotted for the two muscles, and ED_{25}, ED_{50} and ED_{75} values calculated. Each compound was tested in at least five pigs, with the exception of Org 6368 ($n = 4$). Only one compound was administered to each animal. The following values relating to the time profile of neuromuscular blockade were measured:

(a) Onset time: the time from injection to maximum reduction in twitch tension.

(b) Recovery time (25–75%): the time taken for the twitch tension to return from 25% to 75% of the control tension.

(c) Duration time (50%): the time taken from injection for twitch tension to recover to 50% of control.

(d) Duration of action: the time elapsing between drug injection to 90% recovery of control responses.

All time course measurements were made using doses of compounds producing > 75% and < 100% depression of twitch tension, or at 3 × ED_{90} doses.

Maximum drug-induced changes in arterial pressure and heart rate were expressed as both absolute and percent change relative to steady-state pre-drug values.

Results in figures and tables are expressed as mean ± standard errors, with the exception of table I, where potency data are expressed as mean and 95% confidence limits. Statistical analyses of cardiovascular variables were performed using a paired Student *t* test.

RESULTS

Neuromuscular blocking effects

Org 6368, pancuronium and vecuronium produced a non-depolarizing pattern of blockade which was not preceded by twitch augmentation or generalized muscle fasciculations. In contrast, suxamethonium showed a pattern typical of depolarizing blockade.

All compounds blocked preferentially the tibialis rather than the soleus muscle (fig. 1).

An example of composite data on the tibialis muscle is shown in figure 2. Dose–inhibition plots in common with other species were characteristically steep for both muscles. There were no significant differences in the calculated slopes of the regression lines. Analysis of ED_{50} values of the compounds (table I), for example on the tibialis muscle, gave the following relative potencies: pancuronium, 1.0; vecuronium, 0.45; Org 6368, 0.18; suxamethonium, 0.09.

The time profiles of neuromuscular blockade at normal blocking doses (> 75% and < 100% blockade), and three times the ED_{90} dose (calculated from dose–inhibition data on the tibialis muscle), are shown in tables II and III, and a comparison of the time courses is shown in figure 3.

The onset times for neuromuscular blockade at normal doses were shorter on the tibialis than on the soleus muscle. Likewise, recovery times and durations of action were shorter on the tibialis than the soleus. The time course of drug action was in the order: pancuronium > Org 6368 > vecuronium > suxamethonium.

At higher doses (3 × ED_{90}) on the tibialis muscle, the onset times to 100% blockade were rapid and similar for all the compounds. Complete blockade of the soleus was slower to develop than

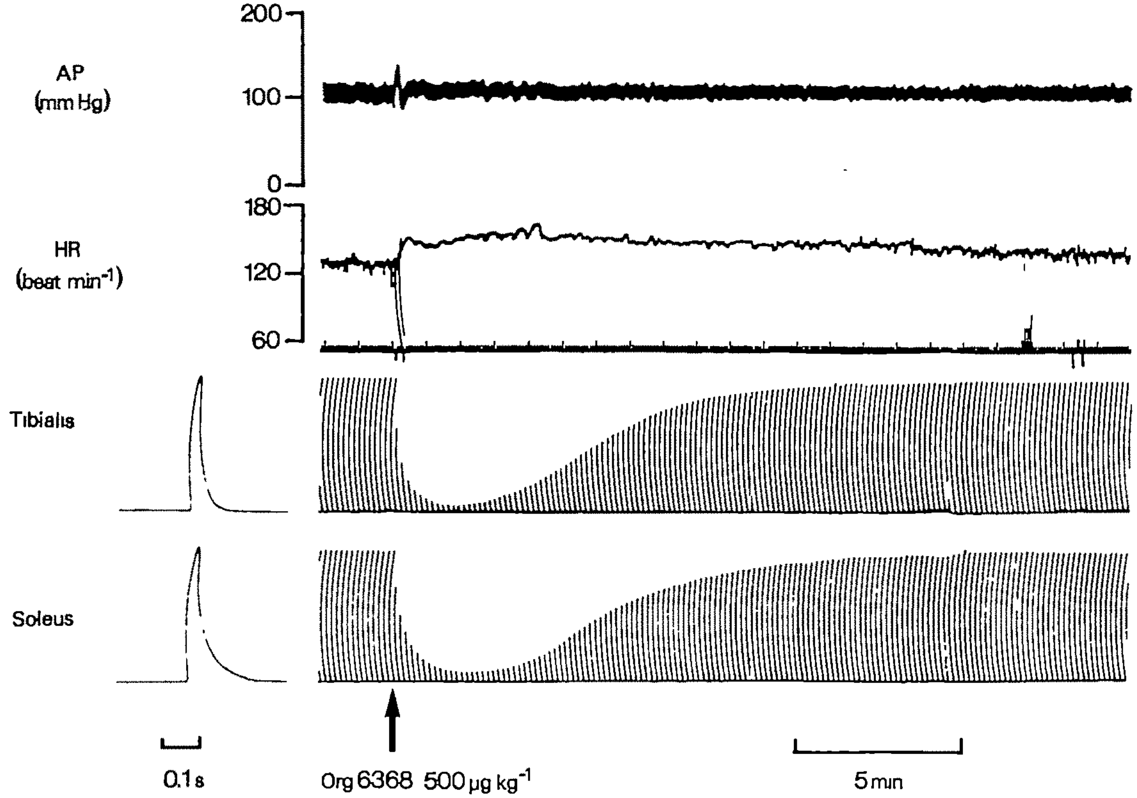

FIG. 1. Effects of an $\simeq$ ED$_{90}$ neuromuscular blocking dose of Org 6368 in the chloralose anaesthetized Landrace–Welsh cross pig. Variables measured were (top to bottom) pulsatile arterial pressure (AP), heart rate (HR) and nerve-evoked twitches of the tibialis (fast) and soleus (slow) muscles.

that of the tibialis muscle, but the soleus muscle showed greater differentiation in onset times between compounds. As expected, at higher doses, the neuromuscular blocking profiles of the compounds were more prolonged, but the durations of action of pancuronium and Org 6368 were increased to a greater extent than those associated with vecuronium or suxamethonium.

Cardiovascular effects of neuromuscular blocking drugs

In chloralose-anaesthetized pigs, the resting (pre-drug) mean arterial pressure and heart rate were 78 mm Hg and 137 beat min^{-1}, respectively.

Cardiovascular changes were investigated in the pigs at normal blocking doses and at 3 × ED$_{90}$

TABLE I. *Neuromuscular blocking potencies of pancuronium, vecuronium, Org 6368 and suxamethonium in the anaesthetized pig. ED$_{50}$ values were obtained from dose–response regression lines constructed by the method of least squares*

	Tibialis			Soleus	
Compound	ED$_{50}$ 95% confidence limits (μg kg^{-1})	ED$_{90}$ (μg kg^{-1})	Slope	ED$_{50}$ 95% confidence limits (μg kg^{-1})	Slope
Pancuronium	33.6 (28.5–38.5)	73.4	118	48.7 (41.1–59.8)	133
Vecuronium	74.7 (70.3–79.1)	141	145	106 (90.9–121)	138
Org 6368	191 (175–207)	388	129	265 (233–306)	157
Suxamethonium	390 (322–450)	750	141	425 (366–482)	128

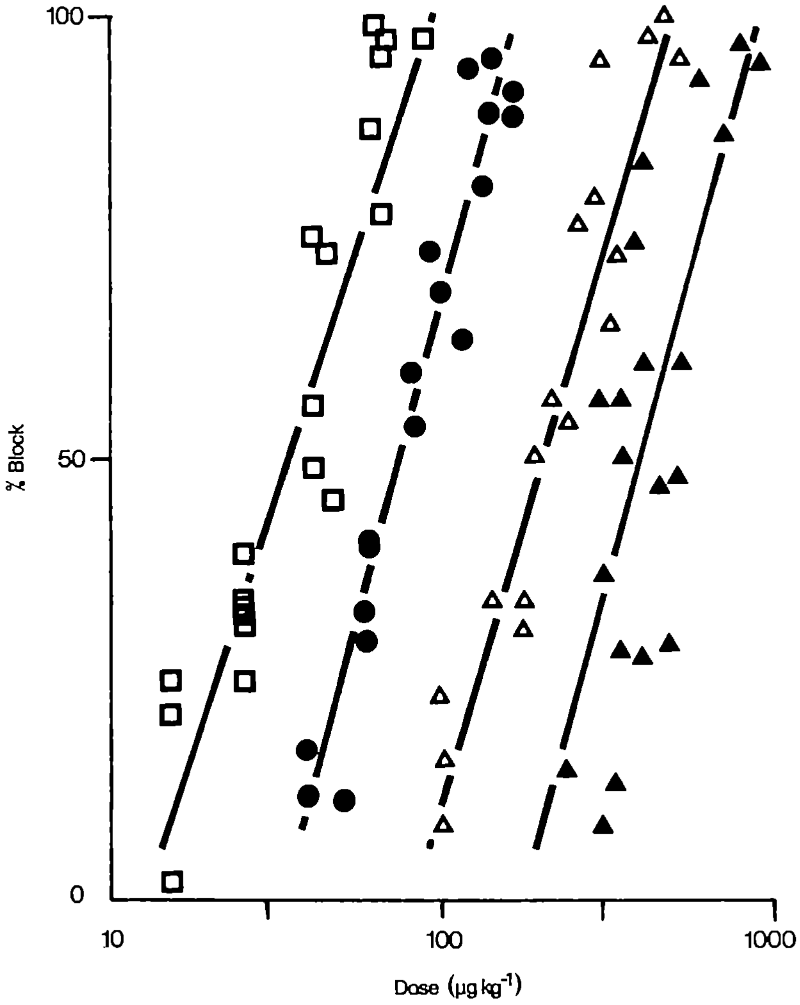

FIG. 2. Dose–inhibition plots on the tibialis anterior muscle for pancuronium (□), vecuronium (●), Org 6368 (△) and suxamethonium (▲) in the chloralose anaesthetized pig. Regression lines were constructed by the method of least squares.

TABLE II. *Time course of neuromuscular blockade (mean ± SEM* (n)) *following the i.v. injection of approximate* ED_{90} *blocking doses of pancuronium, vecuronium, Org 6368 and suxamethonium*

	% Blockade		Onset (min)		Recovery 25–75% (min)		Duration 50% (min)		Duration 90% (min)	
Compound	Tibialis	Soleus	Tibialis	Soleus	Tibialis	Soleus	Tibialis	Soleus	Tibialis	Soleus
Pancuronium	90±4 (7)	91±2 (5)	2.4±0.1	3.1±0.1	5.6±0.6	6.6±1.0	7.3±0.9	10.4±1.5	14.7±1.5	17.6±2.1
Vecuronium	89±2 (9)	86±4 (6)	1.8±0.1	2.4±0.2	3.6±0.4	4.0±0.6	5.1±0.6	6.1±0.8	9.6±1.0	10.9±1.2
Org 6368	91±4 (6)	92±2 (4)	1.8±0.1	2.4±0.1	4.4± 0.4	3.9±0.3	5.9±0.5	7.1±0.9	11.5±0.9	11.8±1.2
Suxamethonium	89±2 (7)	85±2 (7)	0.9±0.1	0.9±0.1	0.4±0	1.1±0.1	1.2±0.1	1.8±0.3	1.7±0.1	3.1±0.3

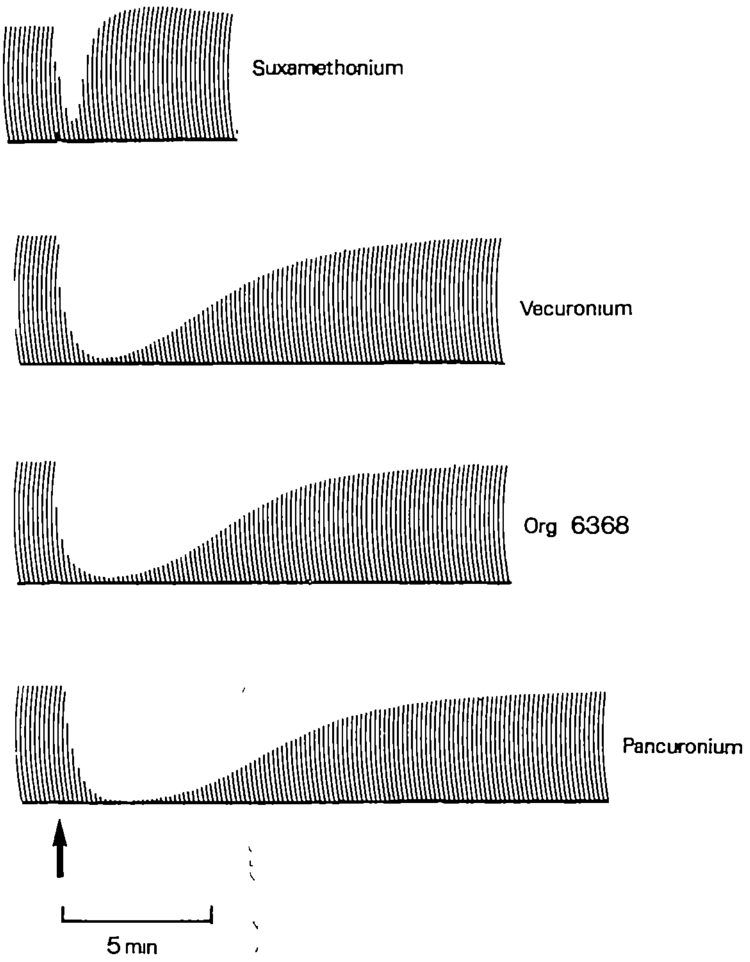

FIG. 3. Comparison of the time-course of action in the pig of pancuronium, vecuronium, Org 6368 and suxamethonium following the administration (at the arrow) of $\simeq$ ED$_{90}$ blocking doses

TABLE III. *Time course of neuromuscular blockade (tibialis muscle) following the i.v. injection of three times calculated ED$_{90}$ blocking doses of pancuronium, vecuronium Org 6368 and suxamethonium in the anaesthetized pig. †Onset from time of injection to 100% inhibition of twitch tension*

Compound	% Blockade	Mean duration of complete blockade (min)	Onset† (min)	Recovery 25–75% (min)	Duration 50% (min)	Duration 90% (min)
Pancuronium ($n = 4$)	100	21.1±1.0	1.3±0.2	14.8±3.0	38.3±2.9	59.5±8.8
Vecuronium ($n = 5$)	100	8.6±0.9	1.3±0.3	5.8±0.4	15.6±1.7	23.4±1.7
Org 6368 ($n = 4$)	100	12.7±3.0	1.0±0.1	6.2±0.5	21.1±2.1	30.7±3.5
Suxamethonium ($n = 5$)	100	1.2±0.1	0.9±0 .	1.8±0.2	4.2±0.4	5.8±0.6

TABLE IV. *Effects of pancuronium, vecuronium, Org 6368 and suxamethonium on mean arterial pressure (mm Hg) in the anaesthetized pig (mean ± SEM* (n)). *Significantly different from pre-drug values using paired* t *test:* $^{*}P < 0.05$; $^{**}P < 0.01$+ $^{***}P < 0.001$

	ED$_{90}$ Blocking doses			3 × ED$_{90}$ Blocking doses		
	Pre-drug	Post-drug	% Change	Pre-drug	Post-drug	% Change
Pancuronium	87±3 (10)	91±3**	+4.9	80±6 (5)	84±4	+4.5
Vecuronium	77±4 (11)	73±4***	−5.6	78±7 (5)	67±6**	−13.9
Org 6368	85±6 (6)	95±8**/ 79±6*	+11.5/−7.1	77±6 (4)	95±10/ 70±5	+22.6/ −10.1
Suxamethonium	79±7 (8)	72±8*/ 115±10***	−9.5/+44.8	73±12 (5)	65±13 121±19**	−10.4/ +65.1

TABLE V. *Effects of pancuronium, vecuronium, Org 6368 and suxamethonium on heart rate (beat* min^{-1}) *in the anaesthetized pig (mean ± SEM* (n)). *Significantly different from pre-drug values:* $^{**}P < 0.01$ *(paired* t *test)*

	ED$_{90}$ Blocking doses			3 × ED$_{90}$ Blocking doses		
	Pre-drug	Post-drug	% Change	Pre-drug	Post-drug	% Change
Pancuronium	135±9 (10)	144±9**	+6.4	139±22 (5)	158±23	+13.7
Vecuronium	126±8 (11)	126±8	0	131±13 (4)	129±15	−1.2
Org 6368	133±9 (6)	145±10	+9.6	149±7 (4)	171±5**	+14.5
Suxamethonium	143±6 (8)	187±9**	+30.6	132±16 (5)	179±14**	+35.3

blocking doses. The effects of the compounds on arterial pressure and heart rate are shown in tables IV and V.

(a) *Normal blocking doses.* Pancuronium produced small transient increases in arterial pressure accompanied by a modest (+9 beat min^{-1}) but more prolonged tachycardia (8–30 min). Following injection, Org 6368 and suxamethonium produced biphasic changes in arterial pressure. Org 6368 caused a transient (3–8 min) decrease in arterial pressure which was preceded by an even shorter increase (+12%). In contrast, suxamethonium induced a small decrease in arterial pressure (0.5–1.0 min) followed by a transient and more marked pressor response (from a mean of 79 to 115 mm Hg). Suxamethonium (+44 beat min^{-1}) and Org 6368 (+13 beat min^{-1}) produced marked and modest tachycardia, respectively, at normal neuromuscular blocking doses, whereas vecuronium did not affect heart rate.

(b) *3 × ED$_{90}$ (tibialis) neuromuscular blocking doses.* Changes in arterial pressure and heart rate at the high doses were generally qualitatively similar, but more marked than at normal blocking doses (> 75 − < 100% block). In particular, at the higher doses the tachycardia induced by Org 6368 (16–60 min) and pancuronium (20–50 min) was prolonged in duration. Even at this high dose, vecuronium did not change heart rate and produced only a small (14%) and transient decrease in arterial pressure.

DISCUSSION

These studies have shown that the anaesthetized pig is a useful additional model for the testing of new neuromuscular blocking agents and shows good cardiovascular and neuromuscular stability over more than 6 h. Pancuronium, vecuronium and Org 6368 all produced a competitive pattern of blockade at the neuromuscular junction, whereas suxamethonium displayed a depolarizing-type blockade which was manifest by fasciculations and pre-blockade twitch potentiation.

In the pig all four compounds were more effective in blocking the evoked twitches of the tibialis than those of the soleus muscle. Suxamethonium (Sutherland et al., 1983) and Org 6368 (Sugrue, Duff and McIndewar, 1975) have, likewise, been shown to be more effective in blocking the twitches of the fast contracting tibialis in the cat. In contrast, vecuronium

(Marshall, Gibb and Durant, 1983) and tubocurarine (Paton and Zaimis, 1951) preferentially blocked the slow contracting soleus muscle in the cat. The relative effect of pancuronium on fast and slow muscles in the cat is more variable as, in some studies, the drug has been found to be more effective in blocking the tibialis muscle (Bonta and Goorissen, 1968), while in others (including our own unpublished results) it blocked more effectively electrically-induced contractions of the soleus muscle. These conflicting findings suggest that there is no marked difference in sensitivity of these muscles to the blocking effects of pancuronium. Interestingly in the pig, in contrast to the cat, the velocities of contraction of the tibialis and soleus muscles were essentially similar (fig. 1).

The order of potency of the neuromuscular blocking agents tested in the pig was pancuronium > vecuronium > Org 6368 > suxamethonium, which agrees reasonably well with their relative potency in man although, in man, unlike most other animal species, vecuronium is equipotent or up to 1.5 times more potent than pancuronium (Krieg, Crul and Booij, 1980; Gramstad and Lilleaasen, 1982).

Suxamethonium displayed very rapid onset and recovery characteristics in the anaesthetized pig even at three times the ED_{90} dose. When compared at 90% neuromuscular blocking doses, vecuronium and Org 6368 possessed similar onset and recovery times which were two to three times those observed with suxamethonium, but about one-half those produced by pancuronium. Interestingly, at higher doses ($3 \times ED_{90}$) the duration of neuromuscular blockade was not increased to the same extent with all compounds, being increased by 2.1- and 2.4-fold with vecuronium and suxamethonium, respectively, compared with 2.8-fold with Org 6368 and 3.4-fold with pancuronium. Thus at $3 \times ED_{90}$ doses, the increasing rank order of duration of neuromuscular blockade was suxamethonium > vecuronium > Org 6368 > pancuronium. These results with Org 6368 in the pig contrast sharply with previous findings with this drug in the anaesthetized cat (Sugrue, Duff and McIndewar, 1975) which showed that Org 6368 possessed significantly (2–3-fold) more rapid onset and recovery characteristics than pancuronium at 90% neuromuscular blocking doses. Subsequent grip-strength studies in human volunteers showed that, although Org 6368 produced a more rapid onset of neuromuscular blockade than pancuronium, their durations of action were very similar (Baird, 1974). Our present results with Org 6368 and pancuronium in the pig agree well with these clinical findings as regards relative potency (1:6), onset time and the duration of neuromuscular blockade produced by these two neuromuscular blocking agents, and suggest that data generated in the pig may be more predictive of the duration of action in man than that obtained in the anaesthetized cat.

The clinical usefulness of a neuromuscular blocking drug depends also upon the degree of separation achieved between its neuromuscular blocking and cardiovascular effects (usually caused by antagonism of cholinoceptors other than those present at the neuromuscular junction (Marshall, 1980)). In man, these cardiovascular effects of neuromuscular blocking agents are usually manifest as tachycardia resulting from a vagolytic action, or in some cases to an additional sympathomimetic effect. In the present study pancuronium and Org 6368 produced dose-related sustained tachycardia which was accompanied by increases in mean arterial pressure, whereas vecuronium did not modify either of these variables. Changes in heart rate in the pig induced by pancuronium and Org 6368 seem to reflect the vagolytic effects of the compounds—as reported in anaesthetized cats (Saxena and Bonta, 1970; Sugrue, Duff and McIndewar, 1975), although part of the effect may also be the result of the release of noradrenaline from cardiac sympathetic nerve endings (Docherty and McGrath, 1978; Marshall and Ojewole, 1979). However, it should be noted that the cardiovascular effects of suxamethonium (hypertension and tachycardia) were much more marked than those caused by the non-depolarizing neuromuscular blocking agents tested.

These preliminary results suggest that the anaesthetized pig represents an additional model in which new non-depolarizing neuromuscular blocking agents may be studied. The time course and potency of the four compounds tested agree well with their reported effects in man and suggest that the pig may provide more reliable time course data than the anaesthetized cat. In addition, cardiovascular effects of drugs like pancuronium and Org 6368 would seem to be easily identified in this model, although the possible vagolytic effects of new compounds should also be studied in the standard anaesthetized cat model.

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DOES A BOLUS OF MANNITOL INITIALLY AGGRAVATE INTRACRANIAL HYPERTENSION?

A Study at Various Pa_{CO_2} Tensions in Dogs†

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SUMMARY

In two groups of anaesthetized dogs, with (n = 28) or without (n = 28) induced intracranial hypertension, we compared the effects on intracranial pressure (ICP) of the rapid administration of mannitol 2 g kg^{-1} i.v. at Pa_{CO_2} 2.7, 4.0, 5.3, and 6.7 kPa (n = 7). In dogs with no induced intracranial hypertension, ICP increased during the administration of mannitol, reached a peak at 2 min after infusion, and then gradually decreased (P < 0.05). More marked changes in ICP were observed in response to higher values of Pa_{CO_2} (P < 0.05). In dogs with induced intracranial hypertension, the rapid infusion of mannitol caused an exponential decrease in ICP, without initial increase, which was significantly steeper at higher values of Pa_{CO_2} (P < 0.05). This was followed by a more gradual decrease which achieved pre-balloon inflation values 10 min after infusion. We postulate that the absence of the initial increase in ICP is the result of (1) a concomitant decrease in arterial pressure, (2) a reduction in the volume–pressure response of the brain, (3) the failure of mannitol to dilate further the cerebral arterial vascular bed and (4) a hitherto unnoticed early water-drawing effect. Our study confirmed the safety of rapidly expanding the circulating blood volume with mannitol in circumstances of increased ICP in dogs.

Ever since hyperosmotic agents, and in particular mannitol, were first introduced for clinical use, the mechanism by which they reduce intracranial pressure (ICP), increase cerebral perfusion pressure (CPP), and enhance cerebral blood flow (CBF) has remained controversial (Johnston and Harper, 1973; Leech and Miller, 1974; Borgstrom, Johannsson and Siesjo, 1975; Brown et al., 1979; Dempsey and Kindt, 1982; Kassell et al., 1982; Muizelaar et al., 1983). Recent evidence suggests, however, that apart from their known water-drawing effect, they may operate by improving microcirculatory dynamics and decreasing cerebrovascular resistance (CVR) (Brown et al., 1979; Burke et al., 1981; Kassell et al., 1981, 1982; Muizelaar et al., 1983; Muizelaar, Lutz and Becker, 1984). Rapidly expanding mass lesions and traumatic head injuries cause profound alterations in the vasomotor tone of the cerebral blood vessels, which progress occasionally to complete vasoparalysis (Langfitt, Weinstein and Kassell, 1965; Langfitt, Tannanbaum and Kassell, 1966; Obrist et al., 1984). In association with such impaired vasomotor tone, autoregulation may be affected and cerebral vasodilatation, accompanied by severe hyperaemia, may ensue (Obrist et al., 1984). As a result, CBF and cerebral blood volume (CBV) are passively augmented, thereby increasing ICP (Miller, 1975; Obrist et al., 1984). Recently, caution has been urged in regard to the use of mannitol during states of increased ICP and lost autoregulation such as occur following traumatic head injury (Jennett and Johnston, 1971; Wilkinson, Wepsic and Austin, 1971; Johnston and Harper, 1973; Cottrell et al., 1977;

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Bruce, 1983; Cohen, 1983; Wilkinson and Rosenfeld, 1983). The reason for this concern is that, in patients with normal ICP, acute increases in ICP have been noted during and after the administration of hyperosmolar mannitol (Cottrell et al., 1977). Researchers have, therefore, suggested (but not demonstrated) that, in patients in whom ICP is increased, mannitol, by increasing CBV early in the infusion, may in fact transiently aggravate the intracranial hypertension (Johnston and Harper, 1973; Cottrell et al., 1977; Bruce, 1983; Cohen, 1983; Wilkinson and Rosenfeld, 1983). On the other hand, hyperventilation is well known to cause cerebral vasoconstriction, thereby decreasing CBF and CBV, and hence ICP. This effect has been shown to take place even in regions with impaired autoregulation (Paulson, Olesen and Christensem, 1972; Obrist et al., 1984).

The present study was undertaken to compare the initial effects of a bolus infusion of mannitol on ICP at various values of Pa_{CO_2} in two groups of dogs: one in which intracranial hypertension had been induced and one in which ICP was normal.

MATERIALS AND METHODS

Surgical preparation

The design of the study was approved by the Montreal Neurological Institute Animal Care Committee. Sixty-two mongrel dogs weighing 18–22 kg were studied. Anaesthesia was induced with a single i.v. dose of sodium thiopentone 12 mg kg^{-1}. A tracheal tube was passed and the lungs ventilated mechanically (Bird mark 7 pressure ventilator; Bird Corp., Palm Springs, Calif., U.S.A.) using compressed air. Ventilation was adjusted to achieve a Pa_{CO_2} of 5.3 ± 0.27 kPa as measured with an infra-red end-tidal $P\text{CO}_2$ analyser. Anaesthesia was maintained with butorphanol tartrate 0.1 mg kg^{-1} i.v. Pancuronium 0.1 mg kg^{-1} i.v. was administered and drugs were repeated as required. Rectal temperature was measured and maintained at 38 ± 1 °C with a thermal blanket. All surgical sites were infiltrated with a 0.25% solution of bupivacaine. A 16-gauge catheter was introduced to the cephalic vein to allow for infusion of maintenance fluid (physiological saline solution 4 ml kg^{-1} h^{-1}) and drugs. A 20-gauge catheter was placed in the femoral artery, under direct vision, to permit the continuous recording of systemic arterial pressure and the sampling of blood. A 20-gauge catheter was inserted through the atlanto-occipital membrane to the cisterna magna to monitor ICP. Arterial and intracranial pressures were measured using previously calibrated Bentley Trantec Model 800 pressure transducers (Bentley Lab., Irvine, Calif., U.S.A.). Continuous recording of heart rate (HR), mean arterial pressure (MAP), ICP and end-tidal $P\text{CO}_2$ were obtained on a Siemens Sirecust 300, four-channel recorder (Siemens AG, Erlangen, West Germany). Arterial blood-gas tensions were determined using a Corning 165/2 pH/blood-gas analyser (Corning Medical, Boston, Mass., U.S.A).

Programme

The animals were divided into three groups. Group A consisted of 28 dogs, subdivided into four subgroups of seven dogs each. Ventilation was readjusted to achieve, in subgroups A_1, A_2, A_3 and A_4, a Pa_{CO_2} of 2.7, 4.0, 5.3 and 6.7 kPa, respectively. Group B consisted of 28 dogs. In all group B dogs the skull was exposed surgically and an appropriate hole made over the parietal lobe for the placement into the extradural space of a 7-French size Fogarty (Edwards Laboratories Inc., Santa Ana, Calif., U.S.A.) venous embolectomy catheter. Group B animals were then subdivided into four subgroups of seven dogs each and their ventilation readjusted to achieve in subgroups B_1, B_2, B_3 and B_4 a Pa_{CO_2} of 2.7, 4.0, 5.3 and 6.7 kPa, respectively. Group C consisted of six control dogs. As in group B, their skull was surgically exposed and an appropriate hole made over the parietal lobe. Pa_{CO_2} was maintained at 5.3 ± 0.27 kPa.

Group A. After a period of stabilization (30 min) baseline measurements of ICP, MAP, and HR were obtained and Pa_{CO_2} values confirmed by the measurement of arterial blood-gas tensions. Following this, a 2-g kg^{-1} dose of a solution of 20% mannitol was infused rapidly over a 5-min period. Data for all animals were collected at 2 min of infusion, at the end of the infusion, and at 2, 5, 10 and 15 min following the cessation of the infusion.

Group B. A balloon was inserted to the extradural space and inflated gradually with 3 ml of air to exert brain compression. There was no effect of the distortion of the CSF pathway on the ICP recording secondary to the balloon inflation. ICP increased to peak values and then decreased gradually. Once a stable and sustained increase in ICP was observed over a 30–40-min period, baseline measurements were obtained and mannitol administered as in group A animals.

Group C. The extradural balloon was inflated to induce intracranial hypertension. However, mannitol was not infused. Measurements of ICP, MAP and HR were taken every 5 min throughout the study period.

Statistical analysis

The results of repeated measures and multiple groups were analysed by one-way analysis of variance. Multiple pairwise comparisons between and within subgroups were assessed by a Bonferroni *t* test (Wallenstein, Zucher and Fleiss, 1980). $P < 0.05$ was considered significant. *P* values are reported only when significant. Data are expressed as the mean ± SEM.

RESULTS

The three groups of animals behaved similarly up to the inflation of the extradural balloon and the administration of the mannitol.

Group A: Dogs with no induced intracranial hypertension

The effects of the infusion of mannitol on ICP, MAP, and HR are detailed in tables I–III and in figures 1–3. Results showed a significant linear

TABLE I. *Changes in ICP (mm Hg) (mean ± SEM) following infusion of mannitol at different* Pa_{CO_2} *in dogs with normal ICP (group A* (n = 28)). *Analysis of variance:* $P < 0.001$. *Multiple pairwise comparisons (Bonferroni)*: *$P < 0.05$ *within subgroups;* †$P < 0.05$ *between subgroups*

Subgroup	Pa_{CO_2} (kPa)	Initial ICP	Baseline	Mannitol infusion 2 min	Mannitol infusion 5 min	After mannitol infusion 2 min	After mannitol infusion 5 min	After mannitol infusion 10 min	After mannitol infusion 15 min
1	5.3	9.0±0.5							
(*n* = 7)	2.7	6.4±0.6	6.4±0.6	6.9±0.6†	7.0±0.8†	7.3±0.7	6.6±0.7†	5.7±0.7†	5.5±0.6
2	5.3	8.6±0.5							
(*n* = 7)	4.0	6.9±0.3	6.9±0.3	8.4±0.4†	10.1±0.5*†	10.3±0.6*†	9.1±0.5*†	7.3±0.4†	5.4±0.2
3	5.3	8.7±0.4							
(*n* = 7)	5.3	8.7±0.4	8.7±0.4	11.4±0.5†	14.3±0.6*†	14.4±0.6*†	13.7±0.6*†	10.4±0.4†	6.4±0.3
4	5.3	8.9±0.6							
(*n* = 7)	6.7	14.1±0.8	14.1±0.8	17.9±0.7†	23.1±0.9*†	23.6±1.1*†	19.9±0.9*†	14.7±0.9†	12.8±0.6†

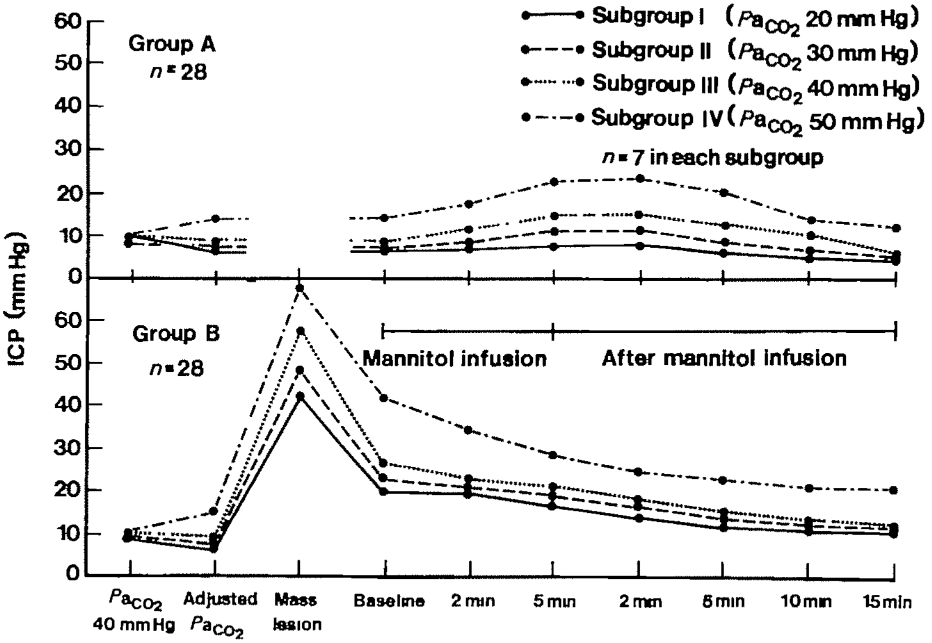

FIG. 1. Mean changes in ICP in groups A and B following mannitol infusion at different values of Pa_{CO_2}. Analysis of variance: $P < 0.001$; multiple pairwise comparisons (Bonferroni) between A and B: $P < 0.05$.

TABLE II. *Changes in mean arterial pressure (MAP) (mm Hg) (mean ± SEM) following infusion of mannitol at different* Pa_{CO_2} *in dogs with normal ICP (group A* (n = 28)). *Analysis of variance:* $P < 0.001$. *Multiple pairwise comparisons (Bonferroni):* *$P < 0.05$ *within subgroups;* †$P < 0.05$ *between subgroups*

Sub-group	Pa_{CO_2} (kPa)	Initial MAP	Base-line	Mannitol infusion 2 min	Mannitol infusion 5 min	After mannitol infusion 2 min	After mannitol infusion 5 min	After mannitol infusion 10 min	After mannitol infusion 15 min
1	5.3	99.4±2.3							
(n = 7)	2.7	104.3±2.2	104.3±2.2	105.4±2.5	112.6±2.1*	114.3±2.7*	114.7±2.4*	107.0±2.0	98.7±2.3
2	5.3	96.9±2.6							
(n = 7)	4.0	101.1±2.3	101.1±2.3	102.2±2.5	112.9±2.4*	113.4±2.5*	110.0±2.3*	105.1±2.4	99.9±2.1
3	5.3	101.0±2.7							
(n = 7)	5.3	101.0±2.7	101.0±2.7	99.8±2.8	107.8±2.6*†	107.6±2.5*†	106.1±2.3*†	102.1±2.9	97.7±2.8
4	5.3	92.7±2.2							
(n = 7)	6.7	113.3±2.3	113.3±2.3	110.7±2.6	126.0±2.7*†	126.1±2.5*†	121.1±2.3*†	113.8±2.2	110.4±2.5

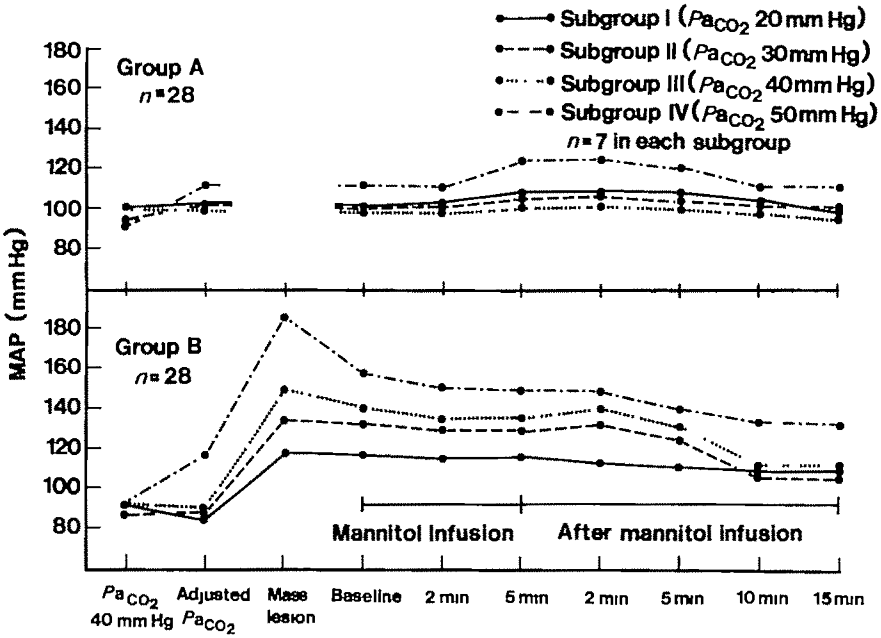

FIG. 2. Mean changes in mean arterial pressure in groups A and B following mannitol infusion at different values of Pa_{CO_2}. Analysis of variance: $P < 0.001$; multiple pairwise comparisons (Bonferroni) between A and B: $P < 0.01$.

trend in subgroups A_1, A_2, A_3 and A_4. ICP increased during the infusion of mannitol, reached a peak at 2 min after the end of the infusion, and then decreased gradually (table I, fig. 1). Higher values of ICP were observed in response to higher Pa_{CO_2} values ($P < 0.05$). Mannitol significantly increased MAP in all animals ($P < 0.05$) (table II, fig. 2); HR transiently increased in group A_4 (table III, fig. 3). Since the effects of mannitol were maximum at 2 min after the end of the infusion, only results derived from that period of time are discussed. Results were compared with baseline measurements.

Group A_1 (Pa_{CO_2} *2.7 kPa*). Mannitol caused a mean 0.9 mm Hg (14%) increase in ICP. MAP increased by 10 mm Hg (9.6%) ($P < 0.05$), and HR declined by 7 beat min^{-1} (5.9%).

Group A_2 (Pa_{CO_2} *4.0 kPa*). Mannitol induced a mean increase of 3.4 mm Hg (49.3%) in ICP ($P < 0.01$). MAP increased by 12.3 mm Hg (12.2%) ($P < 0.05$). HR remained virtually unchanged.

TABLE III. *Changes in heart rate (HR) (beat min⁻¹) (mean ± SEM) following infusion of mannitol at different* Pa_{CO_2} *in dogs with normal ICP (group A* (n = 28)*). Analysis of variance:* $P < 0.001$. *Multiple pairwise comparisons (Bonferroni):* *$P < 0.05$ *within subgroups;* †$P < 0.05$ *between subgroups*

Sub-group	Pa_{CO_2} (kPa)	Initial HR	Base-line	Mannitol infusion		After mannitol infusion			
				2 min	5 min	2 min	5 min	10 min	15 min
1	5.3	123.4±4.9							
(*n* = 7)	2.7	125.5±4.1	125.5±4.1	131.8±4.5	120.3±4.4	118.1±3.0	119.6±3.8	120.7±3.9	122.2±3.7
2	5.3	122.8±3.6							
(*n* = 7)	4.0	127.7±3.5	127.7±3.5	130.1±4.3	124.2±4.6	125.3±4.3	125.5±4.5	125.0±4.4	124.6±4.3
3	5.3	123.8±3.9							
(*n* = 7)	5.3	123.8±3.9	123.8±3.9	121.7±3.0†	118.5±3.7†	119.7±3.6†	120.7±3.7	123.5±3.8	123.1±3.9
4	5.3	120.2±3.6							
(*n* = 7)	6.7	139.7±5.9	139.7±5.9	148.2±5.1†	144.0±4.8†	132.4±4.3†	131.8±4.3	130.4±4.4	132.8±4.6

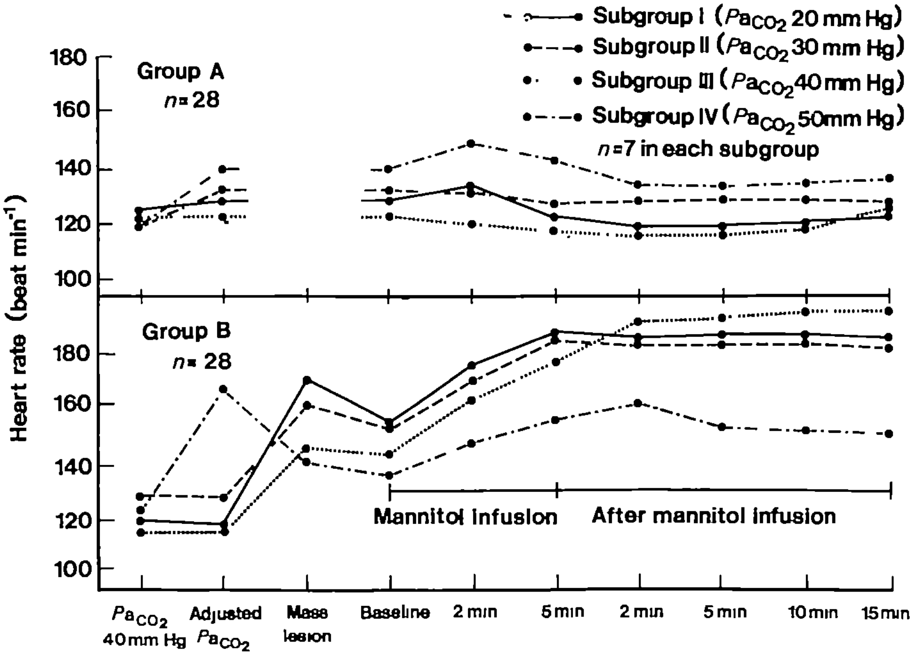

FIG. 3. Mean changes in heart rate in groups A and B following mannitol infusion at different values of Pa_{CO_2}. Analysis of variance: $P < 0.001$; multiple pairwise comparisons (Bonferroni) between A and B: $P < 0.01$.

Group A_3 *(*Pa_{CO_2} *5.3 kPa).* Mannitol caused a mean 5.7 mm Hg (65.5%) increase in ICP ($P < 0.001$). MAP increased by 6.6 mm Hg (6.5%) ($P < 0.05$), and HR decreased by a 4 beat min⁻¹ (3.3%).

Group A_4 *(*Pa_{CO_2} *6.7 kPa).* Increasing the Pa_{CO_2} from 5.3 to 6.7 kPa was associated with a mean increase of 5.2 mm Hg (58.4%) in ICP ($P < 0.001$) and mannitol increased it further by 9.5 mm Hg (67.4%) ($P < 0.001$). MAP increased by 12.8 mm Hg (11.3%) ($P < 0.05$), and HR decreased by 7 beat min (5.2%).

The results of multiple pairwise comparisons for ICP differed significantly between the subgroups for up to 10 min after the cessation of the infusion ($P < 0.05$).

Group B: Dogs with induced intracranial hypertension

Changes in ICP, MAP, and HR are detailed in tables IV–VI, and in figures 1–3. An immediate decrease in ICP without any initial increase characterized the response of this group of animals to the infusion of mannitol ($P < 0.05$) (table IV, fig. 1). Initially, exponential decreases which were significantly steeper at the higher Pa_{CO_2} were observed; these were followed by a more gradual decrease, reaching pre-inflation values 10 min after the discontinuation of the infusion. The systemic haemodynamic response to mannitol consisted of an early, statistically significant, decrease in MAP in subgroups B_3 and B_4 which closely correlated with the early decrease in ICP ($P < 0.05$) (table V, fig. 2). At 2 min after the infusion, MAP increased in subgroups B_2 and B_3 and then gradually decreased in all four subgroups (table V, fig. 2). HR increased significantly in the four subgroups ($P < 0.02$) (table VI, fig. 3). As the most important changes in ICP, MAP, and HR immediately followed the onset of the mannitol infusion, only the results derived during the infusion (at 2 and 5 min) are discussed. Results were compared with baseline measurements.

Group B_1 (Pa_{CO_2} 2.7 kPa). The ICP remained

TABLE IV. *Changes in ICP (mm Hg) (mean ± SEM) following inflation of extradural balloon and infusion of mannitol at different* Pa_{CO_2} *in dogs with maintained intracranial hypertension (group B* (n = 28)). *Analysis of variance* · $P < 0.001$. *Multiple pairwise comparisons (Bonferroni)*: *$P < 0.05$ *within subgroups*; †$P < 0.05$ *between subgroups*

Sub-group	Pa_{CO_2} (kPa)	Initial ICP	Mass lesion	Base-line	Mannitol infusion		After mannitol infusion			
					2 min	5 min	2 min	5 min	10 min	15 min
1	5.3	8.7±0.4								
(n = 7)	2.7	6.5±0.3	43.8±1.5	20.4±1.0	20.0±0.9	17.5±0.9*	14.8±1.2*	12.8±0.9*	11.5±0.8*	11.2±0.7*
2	5.3	8.1±0.4								
(n = 7)	4.0	7.0±0.3	49.1±2.0	23.1±0.9	21.4±0.7	19.1±0.7*	17.1±1.0*	14.5±1.1*	12.2±1.0*	11.5±0.9*
3	5.3	9.0±0.4								
(n = 7)	5.3	9.0±0.4	58.7±1.7	27.5±0.9	23.7±1.1*†	21.1±1.0*†	18.0±0.8*	15.2±0.6*	13.4±0.5*	12.7±0.5*
4	5.3	9.2±0.5								
(n = 7)	6.7	15.1±0.6	68.8±1.7	41.4±1.2	35.7±1.3*†	29.5±1.4*†	25.2±1.2*†	23.2±1.1*†	21.4±1.2*†	21.0±1.2*†

TABLE V. *Changes in mean arterial pressure (MAP) (mmHg) (mean ± SEM) following inflation of extradural balloon and infusion of mannitol at different* Pa_{CO_2} *in dogs with maintained intracranial hypertension (group B* (n = 28)). *Analysis of variance*: $P < 0.001$. *Multiple pairwise comparisons (Bonferroni)*: *$P < 0.05$ *within subgroups*; †$P < 0.05$ *between subgroups*

Sub-group	Pa_{CO_2} (kPa)	Initial MAP	Mass lesion	base-line	Mannitol infusion		After mannitol infusion			
					2 min	5 min	2 min	5 min	10 min	15 min
1	5.3	90.3±3.3								
(n = 7)	2.7	86.5±3.3	123.8±2.6	117.4±2.7	118.4±2.4†	119.1±1.5†	117.7±1.7†	116.2±1.9†	112.5±1.6	112.0±1.8
2	5.3	88.8±3.7								
(n = 7)	4.0	91.0±3.7	136.1±3.3	130.5±3.3	126.3±3.1†	126.4±3.1†	130.7±2.9†	120.7±4.1*	109.0±3.2*	99.4±2.0*
3	5.3	92.2±2.9								
(n = 7)	5.3	92.2±2.9	152.7±1.8	142.5±2.6	136.4±2.5*†	136.0±2.1*†	141.7±2.0†	129.1±2.3*†	114.7±2.3*	111.0±3.1*
4	5.3	94.0±2.7								
(n = 7)	6.7	118.2±2.7	186.5±3.3	157.0±3.3	150.4±3.0*†	148.7±2.7*†	149.5±2.9*†	138.7±2.2*†	130.1±1.8*†	129.2±2.6*†

TABLE VI. *Changes in heart rate (HR) (beat* min^{-1}) *(mean ± SEM) following inflation of extradural balloon and infusion of mannitol at different* Pa_{CO_2} *in dogs with maintained intracranial hypertension (group B* ($n = 28$)). *Analysis of variance*: $P < 0.001$. *Multiple pairwise comparisons (Bonferroni)*: *$P < 0.05$ *within subgroups*; †$P < 0.05$ *between subgroups*

Sub-group	Pa_{CO_2} (kPa)	Initial HR	Mass lesion	Base-line	Mannitol infusion		After mannitol infusion			
					2 min	5 min	2 min	5 min	10 min	15 min
1	5.3	120.4±5.2								
(n = 7)	2.7	118.5±5.9	170.8±6.2	156.1±7.9	175.8±7.0	183.2±4.9*	182.4±5.9*	183.0±5.5*	185.1±5.2*	184.2±4.2*
2	5.3	127.0±4.0								
(n = 7)	4.0	127.8±3.9	160.8±5.6	156.2±6.4	170.5±4.8	181.2±4.9*	181.2±4.6*	183.2±4.3*	184.5±5.1*	181.8±3.6*
3	5.3	116.0±5.3								
(n = 7)	5.3	116.0±5.3	146.4±4.5	142.7±3.8	161.4±3.0*†	177.0±4.0*†	185.0±3.4*†	188.4±2.8*†	190.1±2.6*†	190.5±2.9*†
4	5.3	124.1±3.8								
(n = 7)	6.7	164.1±4.0	142.5±4.6	135.4±4.9	147.2±4.1	158.0±4.7*†	160.4±4.3*†	156.1±5.0*†	153.7±5.0*†	150.8±4.8†

TABLE VII. *Mean (±SEM) changes in ICP, MAP, and HR following inflation of extradural balloon in control dogs with maintained intracranial hypertension (group C (n = 6)). Multiple pairwise comparisons (Bonferroni): no significant differences within the group*

	Initial value	Mass lesion	Baseline	5 min	10 min	15 min	20 min
ICP (mm Hg)	9.3±0.6	54.5±3.1	24.3± 1.5	23.6±1.4	24.5±1.6	25.1±1.6	24.2±1.8
MAP (mm Hg)	88.6±3.3	143.1±3.6	136.5±2.9	137.5±2.8	137.9±3.0	138.4±2.7	138.0±2.6
HR (beat min^{-1})	102.2±4.1	160.8±3.7	138.0±4.4	141.3±4.8	135.2±4.0	142.1±4.3	146.5±3.7

unchanged during the first 2 min of infusion. At 5 min ICP decreased by a mean of 2.9 mm Hg (14.2%) ($P < 0.05$); this decrease was not associated with any significant change in MAP. HR increased at the end of the infusion by 27 beat min^{-1} (17.3%) ($P < 0.02$).

Group B_2 (Pa_{CO_2} 4.0 kPa). At 2 and 5 min ICP decreased by means of 1.7 mm Hg (7.4%) and 4 mm Hg (17.3%) ($P < 0.05$), MAP decreased by 4.2 mm Hg (3.2%) and 4.1 mm Hg (3.1%), and HR increased by 14 beat min^{-1} (9.1%) and 25 beat min^{-1} (16%) ($P < 0.02$), respectively.

Group B_3 (Pa_{CO_2} 5.3 kPa). At 2 and 5 min ICP decreased by a mean of 3.8 mm Hg (13.8%) ($P < 0.05$) and 6.4 mm Hg (23.2%) ($P < 0.01$), MAP decreased by 6.1 mm Hg (4.3%) ($P < 0.05$) and 6.5 mm Hg (4.5%) ($P < 0.05$), and HR increased by 19 beat min^{-1} (13.1%) ($P < 0.01$) and 34 beat min^{-1} (24%) ($P < 0.01$), respectively.

Group B_4 (Pa_{CO_2} 6.7 kPa). Marked decreases in ICP and MAP characterized the onset of the mannitol infusion in this subgroup. At 2 and 5 min, ICP decreased by a mean of 5.7 mm Hg (13.8%) ($P < 0.02$) and 11.9 mm Hg (28.8%) ($P < 0.001$), MAP decreased by 6.6 mm Hg (4.2%) ($P < 0.02$) and 8.3 mm Hg (5.3%) ($P < 0.01$), and HR increased by 11 beat min^{-1} (8.7%) and 23 beat min^{-1} (16.7%) ($P < 0.01$), respectively.

The results of multiple pairwise comparisons for ICP were not significant between subgroups B_1 and B_2, but differed significantly between B_2 and B_3 ($P < 0.05$) and between B_3 and B_4 ($P < 0.001$). Comparing pre-and post-infusion differences in ICP between groups A and B at corresponding values of Pa_{CO_2} revealed consistently a high level of significance ($P < 0.01$).

Control group

At baseline measurements, the untreated control dogs were comparable to group B_3 (Pa_{CO_2} 5.3 kPa) and showed minimal fluctuations in ICP (1–2 mm Hg) over the subsequent 20-min study period (table VII).

DISCUSSION

The dose of mannitol (2 g kg^{-1}) used in this study approximates to the amount recommended clinically for the treatment of head injuries in dogs (Kirk and Bistner, 1981). The use of a small control group was beneficial in that we were able to demonstrate prolonged and sustained stability in ICP, following the induction of the intracranial hypertension at Pa_{CO_2} 2.7, 4.0, 5.3 and 6.7 kPa. Along with the fact that other authors have used similar models to study increased ICP (Sullivan, Miller and Searle, 1980; Dempsey and Kindt, 1982; Wilkinson and Rosenfeld, 1983), this gives additional support to the validity of our method. All animals studied showed a stable ICP for 30–40 min before the mannitol was administered. Thus we were convinced that a reasonable steady-state should have resulted during that period and that the changes in ICP that followed the administration of mannitol were not influenced by haemodynamic events attendent upon the inflation of the balloon.

Many authors have written extensively on the relationship between the rapid administration of mannitol and the possible early aggravation of intracranial hypertension (Jennett and Johnston, 1971; Cottrell et al., 1977; Bruce, 1983; Cohen, 1983; Wilkinson and Rosenfeld, 1983). In the present study, we found important differences in the effect on ICP of the rapid administration of mannitol in dogs with induced intracranial hypertension and in those without. Cottrell and colleagues (1977) compared the ICP-reducing effect of frusemide and mannitol in man, and demonstrated a significant initial increase in ICP in the group of patients to whom mannitol

1 g kg^{-1} was administered. Since no patient had pre-operative clinical evidence of increased ICP, they postulated that, in addition to its effect on CBF, mannitol might have direct vasodilating properties which could also lead to increases in CBV and pressure. Our data from group A animals confirm these findings and allow us to make the following conclusions: (1) The cerebral vasoconstriction induced by hyperventilation attenuated the magnitude of the increases in ICP (groups A_1, A_2). (2) Although there were significant increases in ICP, these never exceeded normal ICP values (15 mm Hg) in the normo- and hypocarbic dogs. (3) Hypercarbia increased significantly the induced increase in ICP. This may be explained by the fact that the increase in Pa_{CO_2} dilates the cerebral vasculature, increases CBV, increases saggital sinus pressure, and alters the mechanical properties of tissues around the CSF spaces (Sullivan, Miller and Searle, 1980). As a result, spatial compensation by means of CSF translocation cannot occur, any replaceable intracranial volume becomes greatly diminished, and the ability of the brain to compensate for additional augmentation in cerebral vasodilatation or CBV becomes limited.

The major finding of the present study was that, in experimental hypertension, bolus use of mannitol decreased ICP readily, did not cause any initial increase in pressure, and was devoid of intracranial side effects at all values of Pa_{CO_2}.

Previous studies of the effect of mannitol on CBF in situations of increased ICP have given conflicting results (Johnston and Harper, 1973; Shapiro, 1975; Brown et al., 1979; Dempsey and Kindt, 1982; Muizelaar et al., 1983; Muizelaar, Lutz and Becker, 1984). Although our study does not address this issue specifically, careful consideration must be given to the impact on the clinical management of patients of the warnings by many authors concerning the effect of the rapid infusion of mannitol to patients with increased ICP (Jennett and Johnston, 1971; Cottrell et al., 1977; Bruce, 1983; Cohen, 1983; Wilkinson and Rosenfeld, 1983). Our results in dogs with intracranial hypertension showed an immediate decrease in ICP in response to the infusion of mannitol. Two separate processes, mediated by two different mechanisms, seem to be involved.

First, we noted that a significant decrease in MAP preceded the early marked decrease in ICP. This may have been caused by the well documented vasodilator properties of hypertonic solutions (Gazitua et al., 1971; Atkins, Wildenthal and Horwitz, 1973; Coté, Greenhow and Marshall, 1979; Krishnamurty, Adams and Willerson, 1979; Stiff, Munch and Bromberger-Barnea, 1979; Findlay et al., 1981). Indeed, the vasodilatation in skeletal muscles, the transient hypotension and the marked shift in the distribution of the cardiac output (Coté, Greenhow and Marshall 1979) may have prevented the increase in CBF and CBV required to produce an increase in ICP. In addition, if the redistribution of cardiac output transiently reduces CBF and CBV, ICP will also be decreased (Davis and Sundt, 1980). In dogs with normal ICP, the injection of mannitol resulted in an increase in arterial pressure, while in the dogs in which ICP was increased, mannitol caused a decrease. The rapid administration of mannitol increases cardiac output (Miller and Sullivan, 1979) and decreases peripheral resistance (Willerson et al., 1975; Coté, Greenhow and Marshall, 1979; Stiff, Munch and Bromberger-Bernea, 1979). As MAP is determined by changes in cardiac output and peripheral resistance, and as profound increases in peripheral resistance have been observed immediately following experimental brain injury (Langfitt, Tannanbaum and Kassell, 1966), we can, therefore, speculate that in the dogs with normal ICP the effect of mannitol on cardiac output predominated and increased MAP, whereas in the dogs with increased ICP the effect of mannitol on the peripheral resistance overrode its effect on cardiac output and decreased MAP. This hypothesis is presently under investigation in our laboratories.

Following this initial decrease, ICP continued to decrease gradually. There are three possible reasons for this further decrease. (1) A reduced volume–pressure response may have permitted more blood volume to be readily accepted by the brain. Indeed, Leech and Miller (1974), in their study of the effects of mannitol on intracranial volume–pressure relationships during experimental brain compression in primates, demonstrated that mannitol reduced the volume–pressure response considerably more than it reduced ventricular fluid pressure (VFP), suggesting that the shape of the volume–pressure curve was altered, thus permitting the intracranial contents to accept a given volume addition more readily. Since this effect appeared earlier and lasted longer than the decrease in VFP, Leech and Miller (1974) emphasized the potential benefit of the administration of mannitol in circumstances of increased

ICP, particularly where the volume–pressure curve is at or near the critical, steeply-increasing stage. (2) In the presence of a reduced cerebral vasomotor tone (Langfitt, Weinstein and Kassell, 1965; Langfitt, Tannanbaum and Kassell, 1966; Obrist, 1984), mannitol may have failed to dilate further the cerebral arterial vascular bed (Johnston and Harper, 1973). (3) In the face of an altered primary vascular response, an early water-drawing effect of the mannitol may have been unmasked (Pappius and Dayes, 1965).

The usefulness of hyperventilation as an adjunct to osmotic diuresis in the treatment of intracranial hypertension is well established (Overguard and Tweed, 1974; Enevoldsen and Jensen, 1978; Obrist et al., 1984). However, of particular interest to our study is the finding by Paulson, Olesen and Christensem (1972) that hypocapnia restores CBF autoregulation in patients with cerebral hyperaemia. This phenomenon may explain the probable recovery of cerebral vasomotor tone in our hyperventilated dogs, which allowed mannitol to dilate directly the cerebral arterial vascular bed independently of changes in cardiac output and MAP, thereby reducing the steepness of the ICP reduction curve (fig. 1).

In conclusion, the commonly held idea of the danger of rapidly infusing mannitol in the presence of intracranial hypertension must be reconsidered. Our animal data validate the safety of this therapeutic procedure and discount the need for any prior manoeuvre to decrease brain size.

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EFFECT OF NITROGLYCERINE-INDUCED HYPOTENSION ON CANINE SPINAL CORD BLOOD FLOW§

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SUMMARY

Twenty-four mongrel dogs were anaesthetized with pentobarbitone and morphine sulphate. Neuromuscular blockade was achieved using pancuronium. Spinal cord blood flow was measured using the radionuclide microsphere and hydrogen washout methods before, during, and following nitroglycerine-induced hypotension. Heart rate, mean arterial pressure, cardiac output, pulmonary capillary wedge pressure, and acid–base balance were determined with each measurement. Mean arterial pressure was reduced by 50%. Spinal cord blood flow, as measured by the microsphere method, increased during the period of hypotension, whereas values obtained using the hydrogen washout method were not significantly different from those at normotension. No significant change in spinal cord blood flow was detected by either method after the application of spinal distraction. Nitroglycerine acts predominantly on venous capacitance vessels and it is postulated that perfusion pressure, and therefore flow, is maintained despite a reduction in arterial pressure.

Controlled hypotension is used during the surgical correction of scoliosis to decrease blood loss and the need for blood tranfusion. Operating conditions are improved and the duration of surgery reduced (McNeill et al., 1974). Sodium nitroprusside and trimetaphan have been recommended as suitable drugs with which to induce hypotension in this situation (Bennett and Abbott, 1977; Lawhon et al., 1984).

Although neurological complications are uncommon following scoliosis surgery (MacEwen, Bunnell and Sriram, 1975), spinal cord injury may result from ischaemia, and there is concern that the interaction between hypotension and spinal distraction could compromise spinal cord blood flow (SCBF). Indeed, a study from this laboratory demonstrated an initial reduction in SCBF when sodium nitroprusside was used to decrease mean arterial pressure (MAP) to 50% of its baseline value (Kling et al., 1985). In addition, nitroprusside-induced hypotension is associated with an increase in circulating catecholamine concentrations and activation of the renin–angiotensin axis (Knight et al., 1983). These may contribute to rebound hypertension and excessive postsurgical bleeding. Tachyphylaxis, cyanide toxicity and death have also been documented with the use of this drug (Tinker and Michenfelder, 1976). Trimetaphan-induced hypotension results in a lesser increase in the concentrations of the stress hormones and it has been suggested that its use may be associated with a lower morbidity (Knight et al., 1983). Thus neither drug would appear to be ideally suited for use in scoliosis surgery.

Nitroglycerine relaxes arteriolar and venous smooth muscle directly and has no direct toxic side effects or toxic metabolites. It produces a smooth and gradual decrease in arterial pressure which is, therefore, easy to control. There is also evidence that the use of beta-adrenoceptor blockade plus nitroglycerine attenuates the hormonal response to induced hypotension (Zadrobilek et al., 1983). When compared with nitroprusside, nitroglycer-

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ine has a favourable effect on myocardial blood flow. Furthermore, during hip surgery, nitroglycerine-induced hypotension is associated with a significantly reduced blood loss (Chiariello et al., 1976; Fahmy, 1978). Since nitroglycerine may have advantages over other hypotensive agents, the aim of this study was to examine its effect on SCBF before, and during, spinal distraction in dogs.

MATERIALS AND METHOD

Twenty-four mongrel dogs (weight 18–28 kg) were anaesthetized with pentobarbitone 30 mg kg^{-1}. Maintenance of anaesthesia was with 50% nitrous oxide in oxygen and morphine sulphate 4 mg kg^{-1}. Pancuronium 0.1 mg kg^{-1} was used to provide neuromuscular blockade. Increments of pentobarbitone 50–100 mg and pancuronium 1 mg were given every hour throughout the procedure which lasted 4–6 h. Ventilation of the lungs was via a Bain breathing system with a fresh gas flow of 3 litre min^{-1} and a tidal volume of 20 ml kg^{-1}, the rate being adjusted to maintain normocarbia (4.9 ± 0.1 kPa) as determined by blood-gas analysis (Radiometer ABL 2). Increments of 4.2% sodium bicarbonate were given to maintain pH within the normal range.

A femoral vein was cannulated to permit the administration of fluids, and a femoral artery was cannulated to allow the direct measurement of arterial pressure (Gould–Statham pressure transducer). A balloon-tipped thermodilution catheter was inserted to the pulmonary artery for the measurement of pulmonary capillary wedge pressure (PCWP) and the determination of cardiac output (CO). Before the induction of hypotension, PCWP was maintained at 8 mm Hg by the infusion of 5% dextrose in lactated Ringer's solution. Cardiac output was measured in triplicate using the thermodilution technique (Electronics for Medicine cardiac output computer). A left atrial cannula was inserted via a limited thoracotomy for the injection of microspheres and the left carotid and right femoral arteries were cannulated to permit the simultaneous withdrawal of samples during the injection of the microspheres. The splenic pedicle was ligated through a midline incision to prevent the canine haemodynamic response to hypotension. Oesophageal temperature was maintained at 36–37 °C using an infra-red heating device. The dog was then turned prone and a laminectomy performed at T7–8. The dura was incised and a platinum electrode inserted 2–3 mm to the spinal cord, midway between its centre and lateral margin. A silver–silver chloride reference electrode was placed in the erector spinae muscles adjacent to the laminectomy. Harrington hooks were fixed at T4 and L2 and connected by an outrigger device.

Haemodynamic indices and arterial blood-gas tensions were measured, before determination of spinal cord blood flow by the hydrogen washout and the radionuclide labelled microsphere methods.

The hydrogen washout method

A 250-µm, Teflon-coated platinum wire, with its tip bared to a distance of 1 mm, was placed as described above. A potential of 650 mV was maintained between the platinum and reference electrodes. Five percent hydrogen was added to the inspired gases for 3–5 min, the current created by oxidation of hydrogen at the electrode tip being recorded as a "wash-in curve" (Gould 2600 chart recorder). The current produced is proportional to the partial pressure of hydrogen at the electrode tip and after the abrupt cessation of the inhalation of hydrogen, a "wash-out" curve was obtained. Hydrogen clearance from the spinal cord was reflected by a decreasing current and, since the blood : tissue coefficient of hydrogen approaches unity, is related to blood flow at the site of the electrode (Auckland, Bower and Berliner, 1964; Griffiths, Rowan and Crawford, 1975).

The platinum electrode was allowed to stabilize for 20 min before two baseline measurements were obtained at normotension. Mean arterial pressure was then reduced to 50 mm Hg using an infusion of nitroglycerine. Two further measurements of spinal cord blood flow were made at 20-min intervals. Following these measurements, 2 cm of spinal distraction was applied by turning the screw of the outrigger device, and 20 min later flow was again measured. Arterial pressure was then restored by stopping the infusion of nitroglycerine and the administration i.v. of lactated Ringer's solution.

The half-life of the wash-out curves was determined by a least squares regression analysis and the plots fitted to a monoexponential decay curve; curves with a correlation coefficient of less than 0.95 were discarded. Eleven out of 24 dogs were eliminated because of unsatisfactory washout curves. The blood flow was calculated from the half-life according to the Fick principle.

The microsphere method

Radionuclide-labelled plastic microspheres may be used for the measurement of organ blood flow (Hales, 1974; Heymann et al., 1977). In the present study, five species of microspheres (cerium-141, chromium-51, ruthenium-103, strontium-85 and scandium-46) 15 µm in diameter were used. Five measurements of SCBF were made: the first with the second hydrogen washout curve at normotension, the second and third at 20 and 40 min following the induction of hypotension, the fourth 20 min after the application of spinal distraction, and the fifth after the restoration of the arterial pressure. All measurements were made simultaneously with the hydrogen washout method. For each measurement, the stock solution was sonically disrupted for a minimum of 30 min and agitated by vortex mixing (Scientific Products S8220 mixer) for a further 5 min before dilution with 10 ml of physiological saline at 37 °C. Starting 15 s before injection and continuing for 2 min afterwards, blood was aspirated from the left carotid and right femoral arteries (reference samples) using a double-barrelled Harvard infusion pump. Microspheres were injected over 30 s to the left atrium using a Sage infusion pump. The syringe and tubing were then flushed with 15 ml of physiological saline. At the end of the study the dogs were killed with potassium chloride, and sections of the spinal cord were obtained at three levels. One section was taken at T7–8, the point at which the platinum electrode was sited, one above this (T2–4) and one below (L2–3). The radioactivity of the tissue and blood samples was analysed using a Tracor 1185 gamma counter. When the femoral and carotid counts differed by more than 25%, mixing was regarded as inadequate. Seven out of 24 dogs were excluded on this basis. In 12 of the 24 dogs, the carotid and femoral counts were within 20% of each other. The average of the two counts was obtained, and flows calculated by using standard equations incorporated to a computer programme.

Mean values for the physiological variables were referenced to the second of the control values obtained with the hydrogen washout method which coincided with the only control value with the microsphere method. Derived values for systemic vascular resistance (SVR) and spinal cord vascular resistance (SCVR) were obtained using standard formulae. SCVR was obtained using SCBF, as measured by the microsphere method at T7–8.

Statistical analysis on the data was performed using Student's *t* test for paired data, and regression analysis as appropriate.

RESULTS

Satisfactory mixing of microspheres was obtained in 17 out of 24 dogs studied and the haemodynamic and acid–base data for these dogs are shown in table I. Mean arterial pressure (MAP) was reduced from 94±5 mm Hg to 48±3 mm Hg. Heart rate increased significantly from 125±6

TABLE I. *Haemodynamic and acid–base values (mean ± SEM (range)) during nitroglycerine-induced hypotension.* n = *17. Values significantly different from control:* * $P < 0.05$; ** $P < 0.01$

		Duration of hypotension			
	Normotension (control)	20 min	40 min	60 min + stretch	Normo-tension
MAP (mm Hg)	94±5 (75–150)	48±3** (35–80)	48±2** (35–65)	49±3** (35–80)	85±3** (60–115)
HR (beat min^{-1})	125±6 (84–175)	167±7** (130–220)	174±6** (130–210)	179±6** (140–240)	168±7** (130–210)
Q (litre min^{-1})	3.2±0.3 (1.0–5.8)	2.9±0.3 (1.3–7.3)	3.3±0.3 (1.5–6.0)	3.6±0.4 (1.4–8.4)	4.7±0.6* (1.8–12.0)
PCWP (mm Hg)	6.2±0.7 (3–15)	6.7±0.9 (4–18)	5.9±1.0 (2–21)	5.8±1.1 (2–21)	8.4±0.9** (3–20)
SVR (dyne s cm^{-5})	2280±553 (1111–1200)	1435±230** (625–4861)	1209±157** (607–3360)	1266±228** (571–4571)	1741±232* (609–4133)
SCVR (T7–8) (dyne s cm^{-5})	578±47 (221–996)	246±21** (136–494)	216±31** (103–646)	190±16** (106–328)	339±49** (110–825)
pH	7.38±0.1 (7.32–7.43)	7.38±0.1 (7.32–7.42)	7.39±0.1 (7.35–7.48)	7.38±0.1 (7.32±7.44)	7.37±0.1 (7.34–7.43)
P_{CO_2} (kPa)	4.9±0.1 (4.3–5.5)	5.0±0.1 (4.5–5.5)	4.9±0.1 (4.3–5.6)	5.1±0.1 (4.7–5.9)	5.1±0.1 (4.6–5.5)

TABLE II. *SCBF (mean ± SEM (range)) (Microsphere) at different spinal cord levels.* n = *17. Values significantly different from control:* *P < *0.05;* ** P < *0.01*

	Normotension (control)	Duration of hypotension 20 min	 40 min	 60 min + stretch	Normotension
SCBF at T2–4	14.0 ± 1.0	15.2 ± 1.2	19.5 ± 1.7**	19.9 ± 1.7**	26.0 ± 3.6**
(ml min^{-1}/100 g)	(9.2–24.1)	(7.7–25.2)	(7.6–32.1)	(10.8–34.8)	(7.1–51.7)
SCBF at T7–8	14.1 ± 1.4	15.9 ± 1.5	19.4 ± 1.7*	20.6 ± 1.6**	31.7 ± 4.5**
(ml min^{-1}/100 g)	(7.6–28.9)	(7.8–29.9)	(7.8–28.9)	(11.3–32.4)	(6.5–55.7)
SCBF at L2–3	21.1 ± 2.5	23.1 ± 2.4	28.9 ± 2.6*	29.3 ± 3.0*	31.7 ± 4.5*
(ml min^{-1}/100 g)	(9.9–52.8)	(11.6–41.6)	(14.8–47.5)	(9.5–56.1)	(6.4–71.7)

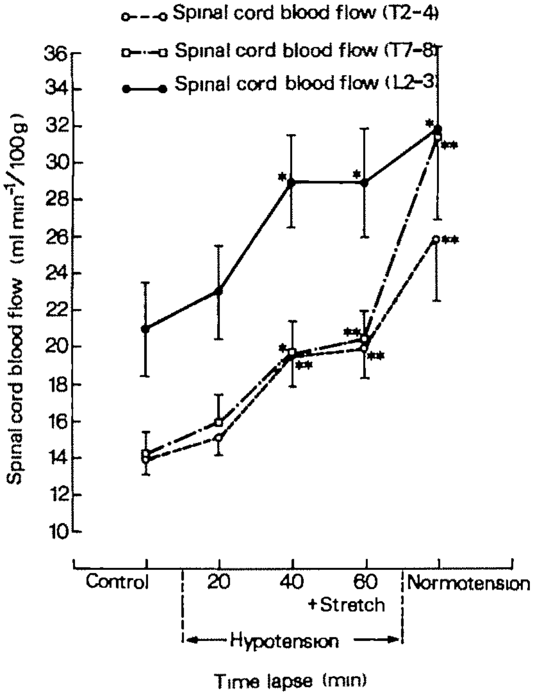

FIG. 1. Spinal cord blood flow as measured by the microsphere method.

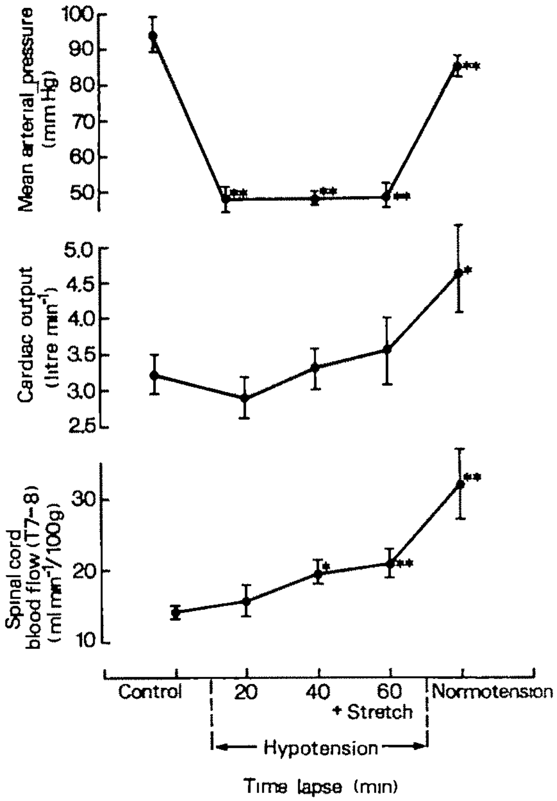

FIG. 2. Mean aterial pressure, cardiac output and spinal cord blood flow at T7–8, before, during and after induced hypotension.

beat min^{-1} to a maximum of 179 ± 6 beat min^{-1} during induced hypotension. The cardiac output and pulmonary capillary wedge pressure were not significantly different from the control values of 3.2 ± 0.3 litre min^{-1} and 6.2 ± 0.7 mm Hg, respectively throughout the period of hypotension, but were significantly increased after the restoration of arterial pressure (4.7 ± 0.7 litre min^{-1} and 8.4 ± 0.9 mm Hg, respectively).

The arterial carbon dioxide tension and pH were not significantly different from the control values of 4.9 ± 0.1 kPa and 7.38 ± 0.1, respectively, throughout the duration of the study.

The spinal cord blood flows determined by the microsphere method are shown in table II. SCBF measured at the three spinal levels was not significantly different 20 min after the induction of hypotension when compared with control values. Thereafter, SCBF was significantly increased when compared with control ($P < 0.05$). Spinal distraction did not affect SCBF adversely.

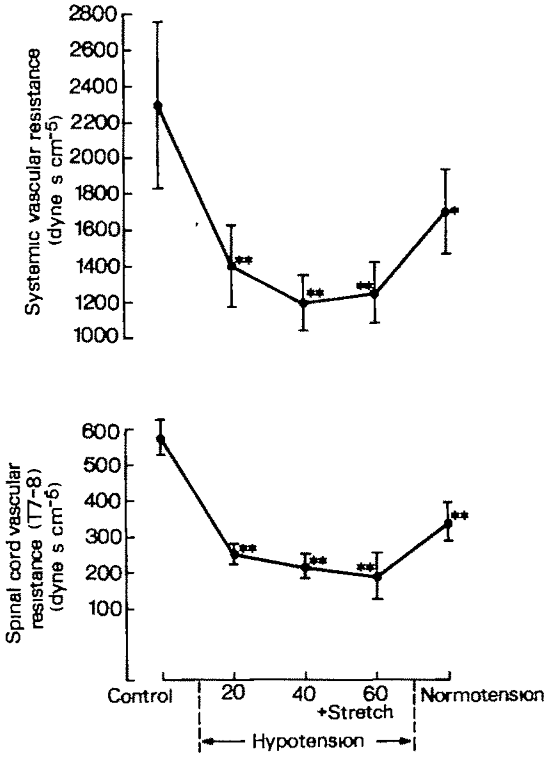

FIG. 3. Systemic vascular resistance, and spinal cord vascular resistance, before, during and after induced hypotension.

These results are shown graphically in figures 1 and 2.

The systemic vascular resistance and spinal cord vascular resistance were significantly decreased during and following the period of induced hypotension when compared with control (fig. 3).

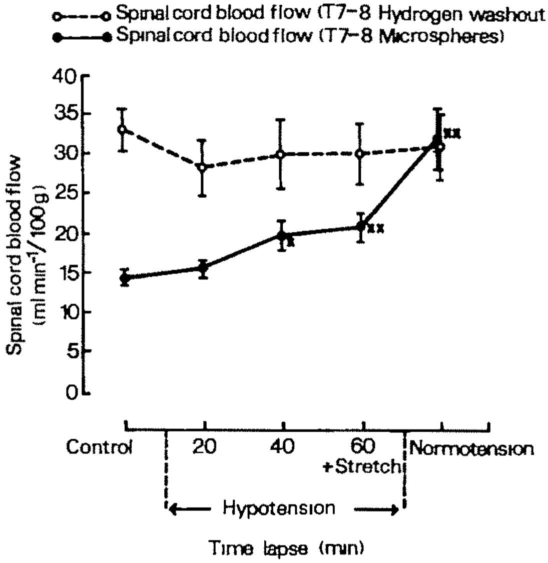

FIG. 4. Spinal cord blood flow at T7–8, as measured by the hydrogen washout and microsphere methods.

SCBF at T7–8, as determined by the hydrogen washout method in a subgroup of 13 dogs, was not significantly different from the control value of 32.8 ± 3.1 ml min^{-1}/100 g throughout the period of hypotension. The results are shown in table III and represented graphically in figure 4, in which the flows obtained by the microsphere method at the same spinal level are also depicted. When the flows obtained by each method were compared, control values obtained by the hydrogen washout method were significantly greater ($P < 0.01$) than those obtained by the microsphere method (32.8 ± 3.1 ml min^{-1}/100 g and 14.1 ± 1.4 ml min^{-1}/100 g, respectively); however, no direct correlation between the two methods was demonstrated.

TABLE III. *SCBF AT T7–8 (mean ± SEM (range)) as measured by either the hydrogen washout or microsphere techniques. Values significantly different from control:* * $P < 0.05$; ** $P < 0.01$

	Normotension (control)	Duration of hypotension			Normo-tension
		20 min	40 min	60 min + stretch	
Hydrogen washout					
SCBF (T7–8)	32.8±3.1	27.7±4.1	30.1±4.6	29.7±4.0	30.8±4.3
(ml min^{-1}/100 g)	(17.6–54.2)	(11.4–59.7)	(10.1–62.4)	(10.3–50.2)	(13.5–73.2)
(n = 13)					
Microsphere technique					
SCBF (T7–8)	14.1±1.4	15.9±1.5	19.4±1.7*	20.6±1.6**	31.7±4.5**
(ml min^{-1}/100 g)	(7.6–28.9)	(7.8–29.9)	(7.8–28.9)	(11.3–32.4)	(6.5–55.7)
(n = 17)					

DISCUSSION

In this study SCBF, as measured by the microsphere method, was unaltered or significantly increased during hypotension with nitroglycerine. Using the hydrogen washout method, no significant change in SCBF was demonstrated during hypotension when compared with control. Furthermore, longitudinal distraction of approximately 6% did not decrease SCBF in the presence of hypotension.

The effect of nitroglycerine on SCBF has not been previously studied. SCBF during hypotension with either sodium nitroprusside (SNP) or trimetaphan has been measured using the xenon-133 clearance technique (Fahmy, Mossad and Milad, 1980). SCBF was relatively constant at MAP values of between 60 and 120 mm Hg during trimetaphan infusion and was increased during SNP infusion. Reduction of MAP to less than 60 mm Hg was associated with parallel reductions in SCBF regardless of the drug used. This is consistent with the findings of another study in which trimetaphan was used to achieve an MAP of 50 mm Hg. SCBF, measured by the microsphere method, was significantly reduced throughout the period of hypotension (Kling, Wilton and Hensinger, 1986). The present study shows that, in contrast to hypotension induced with trimetaphan or SNP, nitroglycerine-induced hypotension was associated with normal or increased SCBF when compared with normotensive values.

Nitroglycerine is a directly acting vasodilator, exerting its effect predominantly on capacitance vessels (Ogilvie, 1978). Its haemodynamic effects during controlled hypotension are well documented (Welter, Fuchs and Herden, 1980). The increase in heart rate seen in this study during the infusion of nitroglycerine is the result of activation of baroreceptor reflexes and a consequent increase in sympathetic activity (Martner and Biber, 1982). Cardiac output and PCWP were not significantly different from control until after the restoration of the arterial pressure. In patients undergoing facial and neck surgery, right and left filling pressures were unaltered during the infusion of nitroglycerine (Zadrobilek et al., 1983) although, in another study, decreases in right atrial pressure and PCWP were observed (Lagerkranser, 1982). Restriction of volume replacement in the latter study probably accounts for these different findings. The persistence of the tachycardia and the decrease in SVR (and SCVR) following the restoration of arterial pressure noted in the present study are the results of a residual nitrate effect.

Nitroglycerine had a favourable effect on regional blood flow in dogs, as determined by the radioactive microsphere method. Cerebral blood flow (CBF) was not significantly reduced despite an MAP of 45 mm Hg (Colley and Sivarajan, 1984). Another study demonstrated that CBF was maintained during nitroglycerine infusion, despite a decrease in cerebral perfusion pressure (CPP), provided cerebrospinal fluid pressure was normal. When cerebrospinal fluid pressure was increased artificially, the reduction in CPP was sufficient to lead to a decrease in CBF (Rogers and Traystman, 1979). When nitroglycerine was administered i.v. to patients undergoing craniotomy, MAP was reduced by 30%, and intracranial pressure was increased. Calculated CPP was significantly reduced (Cottrell et al., 1980). It was concluded that nitroglycerine produces dilatation of venous capacitance vessels within the non-compliant cranial cavity leading to an increase in cerebral blood volume which, if of sufficient magnitude, decreases CBF. A similar mechanism may be operative within the spinal cavity. In our study, cerebrospinal fluid pressure was zero because the dura was opened during the insertion of the platinum electrode used for the hydrogen washout method. Perfusion pressure (PP) would be expected to decrease in proportion to the reduction in arterial pressure. However, the reduction in venous pressure induced by nitroglycerine may offset the decrease in perfusion pressure, and thereby maintain flow. SCBF is therefore unchanged or increased during induced hypotension with the drug.

Several factors influence venous pressure and, therefore, perfusion pressure. In the prone position, the site of the vertebral venous system in relation to the heart reduces venous pressure, whereas inferior vena cava compression and positive pressure ventilation increase it. The net effect is unknown, but nitroglycerine might be expected to contribute to a reduction in venous pressure and thus maintain perfusion pressure.

The mechanisms involved in the autoregulation of SCBF are poorly understood, but the spinal vasculature responds in a manner similar to that of the cerebral circulation, to changes in arterial pressure and blood-gas tensions. In the present study, arterial carbon dioxide and oxygen tensions were maintained within their normal physiological ranges to minimize their effects on SCBF.

Both the hydrogen washout and the microsphere methods were used to measure SCBF in this study. The radionuclide microsphere method relies on the uniform distribution of microspheres and their trapping in the peripheral vasculature. Adequacy of mixing can be assessed by comparisons of carotid (or brachial) and femoral artery counts, major discrepancies being regarded as evidence of poor mixing (Buckberg et al., 1971). In one study, dogs in which differences in the femoral and branchial counts are greater than 25% were excluded (White et al., 1982). Only those dogs in which counts differed by less than 25% were included in the present study and in half of those studied, counts were within 20% of each other. Other authors have recommended comparison of right and left kidney flows (Heymann et al., 1977). In the present study, when kidney flows were compared by paired *t* tests, no significant difference was found. We conclude that mixing was satisfactory, and this is substantiated by comparison of the control values for SCBF in this study with those of other authors (Del Maestro, Schosser and Agerup, 1979; Kozody, Palahniuk and Cumming, 1985).

Our control values for the hydrogen washout method were higher than those of previous studies (Matsumiya and Dohi, 1983; Kling, Wilton and Hensinger, 1986). The explanation for this, and for the discrepancy between control values obtained by each method, is unknown. The hydrogen washout method measures flow at the site of the electrode, whereas the microsphere method measures flow in a transverse section of the cord, so that the two methods are not comparable. Indeed, no statistical correlation between the two sets of data could be demonstrated. This may be attributable in part to the small sample size.

In conclusion, we have demonstrated that SCBF is either unchanged or significantly increased, during hypotension induced with nitroglycerine. Spinal distraction does not affect SCBF, even in the presence of hypotension. No attempt was made to monitor postoperative neurological function, so that the clinical importance of our findings cannot be substantiated. However, nitroglycerine maintains SCBF and, therefore, deserves assessment as a hypotensive agent in patients undergoing the surgical correction of scoliosis.

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POSSIBLE ROLE OF VACUUM SYSTEMS AND COMPRESSED AIR GENERATORS IN CROSS-INFECTION IN THE ICU

A Radioactive Tracer Study

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SUMMARY

Cross-contamination between a hospital's vacuum and compressed air systems was demonstrated using xenon-133 as a tracer. A xenon-133 bolus was introduced to the vacuum system in the intensive care unit. Calculations based on the amount of radioactive tracer recovered from the compressed air outlet at the same location as that at which the tracer was introduced indicated that 17% of the tracer had entered the compressed air system. The contamination was caused because the vacuum and compressed air systems were located in the same machine room. This could conceivably provide a route for respiratory tract contamination in patients receiving ventilatory assistance with air–oxygen mixtures.

Compressed air for medical use has been shown recently to be a potential source of infection in the intensive care unit (ICU) (Bjerring and Øberg, 1986). A mixture of pathogens, and normal skin bacteria, including *Pseudomonas aeruginosa. Bacillus* species, *Corynebacterium* species, *Micrococcus* species and *Staphylococcus epidermidis* were traced to oil-lubricated air compressors. Surprisingly, no limitation on the microbial content of the air supplied directly to seriously ill patients receiving ventilatory assistance with air–oxygen mixtures can be found in the Pharmacopoeia (Pharmacopoea Nordica, 1963), or in the recommendations of the British or International Standards Organisations.

In many hospitals air compressors are situated very close to vacuum compressors in a poorly ventilated machine room. As a result the possibility that bacteria may be transferred from the outlet of the vacuum system to the intake of the compressor used to generate air for medical use should be considered. To verify this possible route of cross-infection we conducted a study, using xenon-133 as a tracer, in a hospital in which the outlets of the vacuum generators were located 1.5 m from the intakes of the air compressors (fig. 1).

MATERIALS AND METHODS

Air containing 19.3 mCi (713 MBq) of xenon-133 was introduced to the hospital's vacuum system, which is used for pharyngeal and tracheal suction in the ICU, at a rate of 42 litre min^{-1} for 5 min. The vacuum storage tank contained 1500 litre and the pipelines approximately 200 litre of air. From the vacuum system xenon-133 was exhausted into the compressor room (50 m^{3}). Room air was drawn

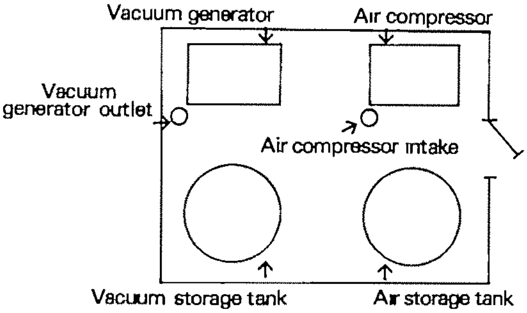

FIG. 1. The compressor room. Distance from vacuum generator outlet to air compressor intake: 1.5 m.

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into the compressors at a rate of 500 litre min^{-1} and stored in a tank (1000 litre) at a pressure of 6.1–8.2 atm. From this tank air was supplied to the peripheral air outlets throughout the hospital.

For measuring purposes air was drawn at a rate of 10 litre min^{-1} from the peripheral outlet at the same location as the suction intake at which the xenon-133 was introduced. Radioactivity was measured continuously by a Xenon monitor 301 (Alnor-MABO, Sweden) calibrated to monitor xenon-133 in the range 0.1–5000 MBq m^{-3}.

RESULTS

Xenon-133 emerged from the air outlet in the ICU approximately 16 min after the tracer bolus had been introduced to the vacuum system. The levels of radioactivity are shown in figure 2. After an initial sharp increase in activity a steady state was attained, allowing calculation of the degree of cross-contamination between the vacuum and compressed air systems. Seventeen per cent of the xenon-133 administered was estimated to have entered the compressed air system.

DISCUSSION

This study has demonstrated the consequences of an engineering design, which allows the mixing of exhaust gases from the vacuum system with the intake for the compressed air generator. The mixing occurred because the vacuum pump and air compressor were housed in the same small room, with only 1.5 m between the outlet of the vacuum system and the compressed air intake. The design of the compressor room is not in conflict with Danish standards, and we have encountered the same arrangement in other hospitals. The reason for this is partly to facilitate servicing and maintenance of the compressors and partly to counteract the problem of noise in the hospital environment.

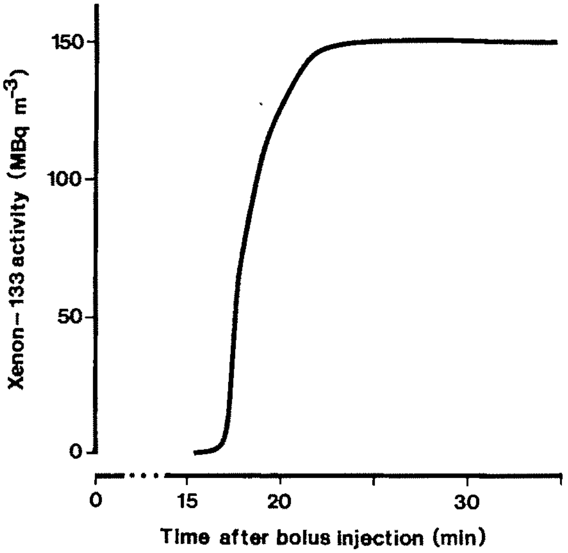

FIG. 2. Activity of xenon-133 detected at the air outlet in the ICU.

This study has demonstrated that it is possible for a gas to be aspirated (from the bedside) into a central suction unit and be returned to the same bedside by way of an air compressor. A radioactive isotope was used as the tracer, because bacteria introduced to the suction system might eventually have reached the lungs of any patients receiving artificial ventilation. Even though xenon-133 gas is more transferrable than a bacteria-containing aerosol, the present study has indicated that compressed air for medical use could be contaminated easily by bacteria from pharyngeal and tracheal suction procedures, and from the operative drainage of infection. In a previous study we were able to demonstrate the presence of pathogens in compressed air used for lung ventilation (Bjerring and Øberg, 1986). In the present study only a small bolus of xenon-133 was injected to the vacuum system; in everyday use the system is contaminated continuously by microorganisms from suction procedures. Over the years the inside of the pipelines and vacuum storage tanks may become lined with a film of microorganism-containing material (Øberg and Bjerring, 1986).

We believe that the practice of locating vacuum and compressed air generators in the same machine room may involve a risk of cross-infection—particularly in the ICU. Infection has been quoted as the most important single factor determining outcome in the intensive care patient (Andersen, 1984) and the airway as the most frequent source of septicaemia (Dominguez de Villota et al., 1983). Whereas a general medical or surgical patient has a 6% risk of becoming infected during his stay in hospital, the risk is 18% in the patient in the ICU (Donowitz, Wenzel and Hoyt, 1982).

The hospital in which we performed this investigation is a centre for the treatment of patients with epidemic diseases like meningitis, severe respiratory tract infections, and the acquired immune deficiency syndrome. Thus the substantial (17%) cross-contamination from the vacuum system to the intakes of the air generators could prove particularly dangerous.

Bacteria present in medical air may also reach pneumatic surgical instruments, which are powered with 200–300 litre of compressed air per minute. During their use at least some of this air is released into the operative field (Øberg and Bjerring, 1985). It is generally accepted that airborne bacteria are responsible for a large number of postoperative infections (Hambreus and Laurell, 1980).

Good engineering practice dictates that the vacuum pump should exhaust outside the compressor room, well away from the intake to the air compressor. The fitting of bacterial filters to the air intakes in the compressor room and to mechanical ventilators is recommended to counteract unnecessary bacterial contamination of the compressed air being supplied to the seriously ill patient.

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PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

LONDON MEETING

NOVEMBER 15, 1986

(The name of the author presenting the paper is shown in bold type. *Indicates non-member.)

EDROPHONIUM IS SHORTER ACTING THAN NEOSTIGMINE WHEN ANTAGONIZING VECURONIUM OR ATRACURIUM

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The authors sought to determine whether edrophonium was as long acting as neostigmine when antagonizing the neuromuscular blocking drugs vecuronium and atracurium in patients anaesthetized with halothane.

After approval by our Hospital Ethics Committee and informed consent, 60 adult surgical patients, ASA class I–II, 18–60 years old were studied. Anaesthesia was maintained with nitrous oxide and halothane. The ulnar nerve was stimulated at 0.1 Hz with supramaximal 0.15-ms pulses; the force of adduction of the adductor pollicis muscle was quantified and recorded. Superimposed on a stable 90% depression of twitch tension induced by vecuronium or atracurium infusion, an i.v. bolus dose of either edrophonium or neostigmine was given. Time required for twitch tension to increase to 50% of peak antagonism and to complete antagonism (onset of action); and to decrease to 70, 50 and then 30% (D_{30}) of peak antagonism (duration of action) were recorded, as was the magnitude of antagonism. Data were analysed by two-factor analysis of variance and analysis of covariance and Student–Newman–Keuls test. Differences were considered significant if $P < 0.05$.

The dose–response curves for edrophonium and neostigmine as antagonists of both neuromuscular blocking drugs were parallel, suggesting that the mechanisms of action of neostigmine and edrophonium are similar. Edrophonium was 12 times less potent than neostigmine, based on ED_{50} values (fig. 1). After equipotent doses, both the onset and duration (D_{30}) were shorter for edrophonium than for neostigmine when antagonizing vecuronium and atracurium. This shorter duration is in contrast to the similar duration of action for these drugs when antagonizing tubocurarine (Cronnelly, Morris and Miller, 1982) and suggests that edrophonium may be less effective than neostigmine when antagonizing vecuronium and atracurium, as compared with tubocurarine.

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THE CARDIFF CUFF CONTROLLER

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Tracheal tube cuff pressures are subject to a variety of constraints· overinflation may lead to tracheal trauma (Seegobin and Van Hasselt, 1984), whereas underinflation may result in leakage past the cuff during ventilation and potential tracheal soiling by gastric contents.

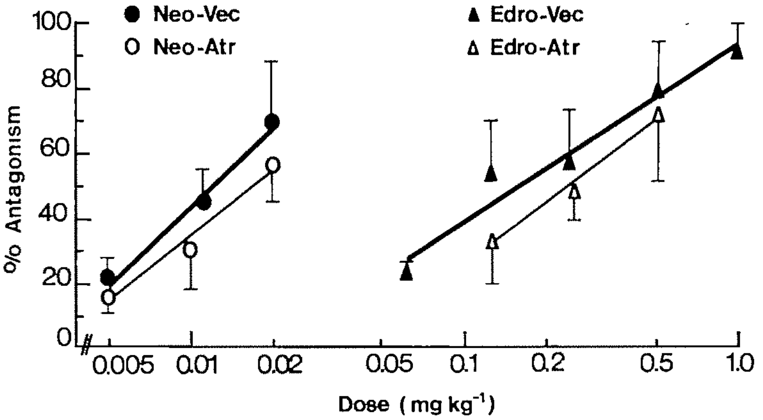

FIG. 1. Dose–response curves of neostigmine (Neo) and edrophonium (Edro) as antagonists of vecuronium (Vec) and atracurium (Atr). Values are mean ± SD.

This study was designed to measure the cuff pressures generated by conventional syringe inflation following intubation and to measure, during anaesthesia, the minimum cuff pressure compatible with the absence of leakage past the cuff. The "Cardiff Cuff Controller" (Morris and Latto, 1985), an electropneumatic device for measuring and maintaining tracheal tube cuff pressures, is described and its clinical application discussed. Tracheal tubes used were Portex standard cuff: 8.0 mm i.d. for adult females, 9.0 mm i.d. for adult males.

One hundred patients undergoing elective surgery were anaesthetized using standard techniques, and were paralysed and ventilated during surgery. The tracheal tube cuff was inflated by a trained assistant using a 10-ml syringe to eliminate leakage. Following inflation the mean cuff pressure was 91 mm Hg (range 9–200 mm Hg); using the cuff controller to vary the cuff pressure it was found that, in the same patients, the mean cuff pressure compatible with the absence of leakage detectable by auscultation over the trachea was 21.7 mm Hg (range 5–100 mm Hg).

The difference between the initial cuff pressure following syringe inflation and the controlled pressure was statistically very highly significant (*t* test, $P < 0.001$) and indicated the need for accurate peri-operative monitoring of tracheal cuff pressures in order that unnecessarily high pressures were not maintained during surgery.

The Cardiff Cuff Controller has been used both in the operating theatre and in the intensive care unit and has been found to be reliable and simple to use.

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VISUAL EVOKED POTENTIAL CHANGES FOLLOWING TRANSURETHRAL PROSTATECTOMY

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FLOW VOLUME LOOPS IN THE EVALUATION OF PATIENTS FOR THYROIDECTOMY

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LUNG FUNCTION DURING REDUCED PULMONARY PERFUSION

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Decreased pulmonary perfusion such as occurs during hypovolaemia or deliberately induced systemic hypotension, is known to increase physiological deadspace/tidal volume ratio ($V\text{D}^{\text{phys}}/V\text{T}$) and the arterial–end tidal $P\text{CO}_2$ difference ($P\text{a}_{\text{CO}_2}-P\text{E}'_{\text{CO}_2}$) (Eckenhoff et al., 1963; Freeman and Nunn, 1963). The major change is an increase in the alveolar deadspace fraction, $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$. Alveolar deadspace is difficult to measure, and we do not know to what extent changes in it are reflected in changes in the more easily measured ($1-P\text{E}'_{\text{CO}_2}/P\text{a}_{\text{CO}_2}$) when pulmonary perfusion is reduced. The relationship between the two is only approximate even during normovolaemia (Fletcher and Jonson, 1984). To study this relationship we observed, on a breath-by-breath basis, the changes in carbon dioxide elimination that occur when cardiopulmonary bypass (CPB) is instituted, that is, when pulmonary artery flow and pressure are reduced.

Carbon dioxide single breath tests ($\text{SBT}-\text{CO}_2$) were recorded using an on-line computerized system based on the Servo ventilator. There were seven male patients, mean age 57 yr, undergoing coronary artery bypass grafting and one female, aged 67 yr, undergoing mitral valve replacement. When partial CPB was started, the surgeon was asked to delay going on total CPB until a series of breaths, with $P\text{E}'_{\text{CO}_2}$ decreasing to 1–2 kPa, had been registered. Values for $1-P\text{E}'_{\text{CO}_2}/P\text{a}_{\text{CO}_2}$ and $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ were calculated as if $P\text{a}_{\text{CO}_2}$ had remained constant throughout the experiment. (This does not quantitatively affect the observations or conclusions.)

As pulmonary perfusion was reduced ($P\text{a}_{\text{CO}_2}-P\text{E}'_{\text{CO}_2}$) increased. The slope of phase III of $\text{SBT}–\text{CO}_2$ remained constant, however, so that the relationship between $1-P\text{E}'_{\text{CO}_2}/P\text{a}_{\text{CO}_2}$ and $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ improved ($P < 0.01$). Mean airway deadspace, $V\text{D}^{\text{aw}}$, decreased by 10 ml ($P < 0.01$). A decrease in $V\text{D}^{\text{aw}}$ is known to occur *after* CPB, in association with the large post-CPB reduction in functional residual capacity (FRC). (Related changes in $V\text{D}^{\text{aw}}$ and FRC have also been observed in other situations, such as thoracotomy.) Preliminary results suggest this reduction occurs suddenly. However, if FRC is not altered immediately after institution of CPB, other mechanisms, hinging on regional differences, must be sought for the reduction in $V\text{D}^{\text{aw}}$. During hypoperfusion, only dependent lung regions receive blood. Because carbon dioxide is eliminated only from ventilated, perfused regions the $V\text{D}^{\text{aw}}$ registered will be less than the "whole lung" $V\text{D}^{\text{aw}}$, if these dependent units empty preferentially early in expiration. A further possible mechanism is that dependent regions have the smallest regional lung volume, which may be reflected in a reduced $V\text{D}^{\text{aw}}$.

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INFLUENCE OF THIOPENTONE SEDATION AND ANAESTHESIA ON SCALENE MUSCLE ACTIVITY

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CALCIUM REVERSES VERAPAMIL–HALOTHANE INDUCED REGIONAL MYOCARDIAL DYSFUNCTION

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Verapamil is recommended in coronary artery disease for its antiarrhythmic and coronary antispasmodic properties. In combination with volatile anaesthetics, verapamil may cause asynchrony of contraction even in myocardium with a normal blood supply (Ramsey et al., 1986). Calcium chloride can reverse the cardiovascular depressant effect of verapamil without altering its electrophysiological actions (Haft and Habbab, 1986). We wondered whether calcium chloride would reverse the verapamil-induced regional dysfunction.

In six unpremedicated sheep anaesthesia was induced with thiopentone and, after tracheal intubation and normocarbic IPPV, maintained with 1.2% inspired halothane. A left thoracotomy was performed, the heart exposed and two pairs of piezoelectric crystals were implanted in the territories of the left anterior descending (LAD) and left circumflex (LC) coronary arteries to measure myocardial segment length. Aortic and left ventricular cannulae were placed for monitoring systemic and left ventricular pressures, and electrodes attached to monitor Lead II of the electrocardiogram. Following a 1-h stabilization period, the effects of four cumulative doses of verapamil 0.04, 0.08, 0.16 and 0.32 mg kg^{-1} were studied. Calcium chloride 5 mmol was then administered and its effects recorded. Data were analysed with two-way analysis of variance and Duncan's test, with $P < 0.05$ considered significant.

Cumulative doses of verapamil caused a significant decrease in LAD systolic shortening, the appearance of LAD dysfunction as post-systolic shortening (table I), and significant increases in the P–R interval. Calcium chloride significantly improved LAD systolic shortening (SS) and abolished the LAD post-systolic shortening (PSS), without lessening the prolongation of the P–R interval.

TABLE I. *Effects of verapamil and calcium on regional myocardial function and AV conduction.* *P < 0.05 *v. control;* +P < 0.05 *v. verapamil*

	Control	Verapamil 0.32 mg kg^{-1}	Calcium
SS (%)	21.5 ± 2.6	$11.4 \pm 2.9^{*}$	$21.1 \pm 3.0^{+}$
PSS (%)	1.6 ± 1.6	$13.6 \pm 12.0^{*}$	$0.8 \pm 0.8^{+}$
PR (ms)	107 ± 5	$157 \pm 5^{*}$	$150 \pm 13^{*}$

While the administration of calcium chloride has been shown to reverse verapamil-induced global haemodynamic depression without affecting verapamil's electrophysiological properties (Haft and Habbab, 1986), in this study calcium chloride reversed the verapamil-induced decrease in regional function and, more importantly, reversed the regional dysfunction. Thus calcium chloride is effective in reversing both the global and regional effects of verapamil while preserving its effect on AV conduction.

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COMPARISON OF ATRACURIUM-INDUCED NEUROMUSCULAR BLOCKADE IN NEONATES, INFANTS AND CHILDREN

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Although the pharmacology of atracurium has been studied in infants (Brandom et al., 1984) no comparable data are available for neonates. In the present study the ED_{50} and the ED_{95} of atracurium were determined under thiopentone–fentanyl–nitrous oxide anaesthesia. In addition, the duration of action of a standard intubating dose was determined.

Sixty-three patients, 21 neonates (aged 1–28 days), 21 infants (aged 1 month–1 yr) and 21 children (aged 1–5 yr) were the subjects of the study. No premedication was given. Anaesthesia was induced with thiopentone 6–8 mg kg^{-1} and fentanyl 5 μg kg^{-1} and maintained with nitrous oxide, oxygen and further thiopentone as required. Intubation of the trachea was performed without muscle paralysis and ventilation was adjusted to maintain normocarbia. The ulnar nerve was stimulated supramaximally at the wrist using a train-of-four (TOF) sequence at 2 Hz repeated every 10 s. The resulting force of thumb adduction was measured and recorded.

Three sub-groups of five neonates received atracurium in boluses of 65, 85 or 100 μg kg^{-1}; three subgroups of infants received 85, 100 or 150 μg kg^{-1}, and three subgroups of children received 100, 150 or 200 μg kg^{-1}. Linear dose–response curves were obtained by log-angular transformation of the data and the ED_{50} and ED_{95} of atracurium were calculated by substitution in the regression equations. Six patients from each group received atracurium 0.5 mg kg^{-1} and the time taken for the first twitch (T1) of the TOF to recover to 10% of the control twitch height was measured. Recovery times are given as mean ± SEM and significance was determined using Student's *t* test.

For neonates the ED_{50} of atracurium was 79 μg kg^{-1} and the ED_{95} was 109 μg kg^{-1}; for infants the ED_{50} was 115 μg kg^{-1} and the ED_{95} was 155 μg kg^{-1}; for children the ED_{50} was 137 μg kg^{-1} and the ED_{95} was 191 μg kg^{-1}. The times to 10% recovery of T1 were 22.1 ± 1.5 min for neonates, 29.7 ± 2.4 min for infants and 28.6 ± 0.6 min for children. The differences between the neonates and the other two groups were statistically significant ($P < 0.05$ and $P < 0.01$, respectively).

These results indicate that neonates are "sensitive" to atracurium and require less drug to produce a given degree of neuromuscular block. However, recovery may be more rapid following a standard intubating dose of 0.5 mg kg^{-1}.

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MEASUREMENT OF PREOPERATIVE ANXIETY IN RELATION TO ANAESTHESIA

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Despite the growing realization of the relationship between preoperative anxiety and postoperative welfare and the knowledge that emotional factors may initiate severe physiological reaction, little attention has been paid to anxiety in relation to anaesthesia. This work had two major aims: to establish a technique for the quantification of the body's response to transient anxiety and to explore the amount of anxiety induced in preoperative patients in relation to anaesthesia and surgery.

The method of quantification of anxiety used in this study was the estimation of palmar sweat changes by means of an evaporimeter. Previous work had shown that this instrument is highly suitable for the measurement of stress induced by a specific factor such as discussion of surgery and anaesthesia (Nilsson, 1982; Bishop, 1983) and correlates well with changes in the heart rate, an established index of stress under general anaesthesia ($r = 0.83$: $P < 0.001$). Other variables measured in conjunction with palmar sweat were heart rate, bi-polar analogue scales, clinical assessment and Spielberger's self-evaluation questionnaire.

One hundred and forty-two patients in a district hospital were studied. The results obtained from all the techniques used, with the exception of the Spielberger questionnaire, fell within a normal distribution and were analysed by the unpaired Student's t test A highly significant increase in evaporimeter measurements ($P < 0.004$) was shown in relation to the topic anaesthesia which was not demonstrated in the subjective measures used. Correlation between physiological and subjective measures was poor, as was correlation between the subjective measures.

The results of this study demonstrate that fear of anaesthesia is a major component of preoperative anxiety and discriminating intervention to allay these anxieties is recommended.

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CARDIOVASCULAR AND PALMAR SWEAT CHANGES IN PATIENTS UNDERGOING CYSTOSCOPY

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Rapid, quantitative, non-invasive assessment of the degree of sympathetic response to stressful stimuli is currently limited to the measurement of heart rate and arterial pressure. The sympathetic response to stress also includes the production of palmar sweat, which can be measured using the Servo Med evaporimeter (Maryniak and Bishop, 1987). We have evaluated the production of palmar sweat and its correlation with heart rate during anaesthesia and surgery.

Heart rate, arterial pressure and palmar sweat production was determined in a total of 43 patients scheduled for cystoscopy. Following premedication with diazepam 10–20 mg, anaesthesia was induced with thiopentone 4 mg kg^{-1} and maintained with 1–2% halothane and 66% nitrous oxide in oxygen. The control group (A) consisted of 22 patients. Following baseline measurements, values were taken at insertion of the indwelling needle after administration of thiopentone, and at 1-min intervals to 8 min. The 21 patients in group B received an identical anaesthetic, but 5 min after induction of anaesthesia the patient was put into the lithotomy position and at 7 min cystoscopy was performed. In this group measurements were also made at the end of the procedure and at recovery from anaesthesia.

Mean heart rate and palmar sweat production increased significantly in both groups following induction of anaesthesia. Mean heart rate returned to control at 5 min, mean sweat production 7 min after thiopentone. There were no significant differences in heart rate and palmar sweat production at comparable times between the two groups. Mean arterial pressure began to decrease in the control group 5 min after induction of anaesthesia and became statistically significant from the cystoscopy group after 6 min. A good correlation was found between the mean heart rate and the mean palmar sweat production of all 43 patients ($r = 0.83$; $P < 0.001$).

We conclude that the measurement of palmar sweat production may be a useful, sensitive and non-invasive method of assessing the degree of sympathetic activity during anaesthesia and surgery.

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HAS PROPOFOL AN ANTI-EMETIC ACTION?

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A distinct impression has been formed that the incidence of postoperative sickness was very low following the use of propofol. A retrospective analysis of data from 200 women anaesthetized with propofol for minor operations showed that only three were nauseated and none vomited in the first 1 h after operation. As this is a lower incidence than reported in similar patients anaesthetized with barbiturates (Dundee et al., 1965, 1970) it prompted a comparative study of the emetic sequelae in comparable patients anaesthetized with propofol and methohexitone. A recent study reported no significant difference in emetic sequelae following these drugs in unpremedicated patients undergoing outpatient dental operations (Valanne and Korttila, 1985).

Our study involved 80 women undergoing minor gynaecological operations lasting 5–15 min. In random order, equal numbers were premedicated with morphine 7.5 mg or pethidine 75 mg i.m. 60–120 min before induction. Half of the patients (20) in each group were anaesthetized with propofol with 66% nitrous oxide in oxygen and for the other half propofol was replaced by methohexitone. No volatile agents were used and none required any postoperative medication.

Frequent pre- and postoperative visits were made to patients when the occurrence of nausea (N) and vomiting, with or without nausea (V) was noted. The significance of the difference between various groups was calculated by Fisher's exact probability test.

After morphine premedication the incidence of emetic sequelae was significantly lower when anaesthesia was with propofol (table II). The trend was similar, but less marked with pethidine 75 mg.

Of the patients nauseated before operation (table III), in the first 1 h after operation significantly more had nausea and vomiting after methohexitone than after propofol, but the difference had passed by 6 h.

TABLE II. *Emetic sequelae in patients premedicated with morphine 7.5 mg.* *N *and* V *combined in calculating the* P *value*

	Time after op. (h)					
	0–1			1–6		
Anaesthesia	V	N	—	V	N	—
Methohexitone	2	6	12	4	9	7
Propofol	0	0	20	3	2	15
*P**	0.0033			0.0248		

TABLE III. *Incidence of postoperative sickness in patients who were nauseated by premedication*

Anaesthesia	Preop. nausea	Postop. V and N	
		0–1 h	1–6 h
Methohexitone	6	4	2
Propofol	7	0	1
P		0.042	0.874

This study demonstrates that women premedicated with two opioids had fewer emetic sequelae following short minor gynaecological operations following propofol anaesthesia than after methohexitone.

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COGNITIVE FUNCTIONING IN ANAESTHETISTS

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A number of studies have reported impaired psychological functioning following acute exposures to subanaesthetic concentrations of anaesthetic agents (Smith and Shirley, 1978). However, the extrapolation of study results to an occupational setting is indirect because student volunteers have been exposed in a laboratory setting. The present study used a more direct approach by examining the cognitive functioning of anaesthetists working in actively scavenged operating theatres.

Twenty-two anaesthetists (mean age 34 yr; range 25–55 yr) were seen on two separate days in a cross-over design: one day in a suitable reference condition (e.g. ITU) and one day in an actively scavenged operating theatre. Eleven subjects worked in theatre on the first day and 11 worked in the reference condition on the first day. On each day, time-weighted average exposure to nitrous oxide and halothane was measured using personal monitors working in the passive mode (O'Sullivan, Holdsworth and Musgrave, 1982) and subjects attended three testing sessions lasting 30 min: before work, in the middle of the day and after work. At each testing session concentration of halothane in end-tidal air was measured and anaesthetists completed a sequence of computer controlled tasks assessing major cognitive functions.

Exposure to nitrous oxide and halothane in the actively scavenged theatres averaged 58 and 1.4 p.p.m., respectively, and end-tidal concentrations of halothane were about 1 p.p.m. greater at the time of testing. These levels of exposure are equivalent to the lowest used in previous laboratory studies. The fairly comprehensive psychological investigation included a mood checklist and tasks assessing memory, verbal reasoning and sustained attention. The sensitivity of the tasks to the cognitive functions under investigation was reflected in the effects of (a) syntactic and semantic factors on verification speed and accuracy in verbal reasoning tasks, (b) memory load on recognition speed and accuracy in a spatial memory task, (c) processing difficulty on recall levels in a verbal memory task and (d) task duration and signal uncertainty in a sustained attention task. However, there was no evidence for impairment of cognitive functioning relating to acute exposure to anaesthetic agents. Task performance, however, was influenced by work demands, the degree of work control and self-reported stress.

Anaesthetists reported higher stress levels after long work hours and more demanding work, but scores were not influenced by exposure. By contrast, anaesthetists felt more aroused when their work was less demanding and more under their control, and scores peaked during the middle of theatre days. It seems likely that the greater "alertness" in the middle of the exposed day reflects the nature of operating theatre work. It is concluded that cognitive functioning is unlikely to be impaired by exposure to the small concentrations of anaesthetic agents found in actively scavenged operating theatres.

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EFFECTS OF DIAZEPAM, KETAMINE, MORPHINE AND NALOXONE ON THE UPTAKE OF POTASSIUM INTO ASTROCYTES

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Primary cultures offer the opportunity to study the effects of drugs in intact cells of a single type. Astrocytes make up approximately one-third of the cellular volume of the brain cortex in man and appear to regulate intracelluar K^+ homeostasis by actively accumulating the K^+ released by excited neurones. The barbiturates inhibit this process and this may be related to their anaesthetic action. We decided to assess the effects of diazepam, ketamine, morphine and naloxone on the active uptake of K^+ by astrocytes in primary culture.

Primary cultures of mouse astrocytes were prepared in a manner described in detail elsewhere (Hertz, Juurlink and Szuchet, 1985). The cultures consisted of 95% astrocytes and 5% other elements and formed a confluent monolayer adhering to the base of the culture plates. Uptake was measured in astrocytes that had been depleted of intracellular K^+ by preincubation in ice-cold K^+-free modified Eagle's medium (MEM) for 30 min before the experiment. This effectively prevents the possibility of homoexchange and reduces substantially the electrochemical gradient driving K^+ into the cells, allowing exclusive measurement of active net uptake. Each culture was washed twice with K^+-free MEM and then floated on a water bath maintained at 37 °C. Warm medium (37 °C) containing ^{42}potassium 1–2 µCi (total potassium 6.6 mmol $litre^{-1}$) was added and the cultures incubated for 10 s. The test drug was added simultaneously. Uptake rates were calculated from the uptakes of potassium-42 into the tissues and the specific activities of the media. Protein content was determined using the conventional Lowry technique. Results are as shown in table IV.

TABLE IV. *Results: Potassium uptake (nmol min^{-1}/mg protein) (mean ± SEM).* n = *8;* *$P < 0.01$*;* **$P < 0.001$

	10^{-3} mol $litre^{-1}$	10^{-6} mol $litre^{-1}$
Control	809 (27)	1029 (56)
Diazepam	515 (18)**	771 (57)*
Ketamine	—	942 (81)
Morphine	687 (32)*	928 (34)
Naloxone	786 (41)	922 (24)

It can be seen that diazepam at both concentrations tested significantly reduced the active uptake of K^+ into the cells. Morphine caused a statistically significant reduction at 10^{-3} mol $litre^{-1}$ but was ineffective at 10^{-5}. Naloxone and ketamine had little effect.

Alteration of the extracellular space (ECS) K^+ concentration can have significant inhibitory or excitatory effects on neuronal activity. Our data indicate that diazepam may act by inhibiting astrocytic K^+ uptake and so alter ECS [K^+]. The effect of morphine probably represents a non-specific membrane effect. I.v. anaesthetics have many different mechanisms of action; diazepam and perhaps others may act by inhibiting K^+ uptake by astrocytes.

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HEART RATE CHANGES IN ANAESTHETISTS AND SURGEONS

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A simultaneous comparison of heart rate and arrhythmias between anaesthetists and surgeons during operative procedures has not been documented previously. The objective of this study was to record the time and degree of maximal stress experienced by both groups and ascertain if it varied with the time of surgery or experience of personnel.

Twenty-four anaesthetists and surgeons (12 in each group) were Holter monitored throughout an entire operating list using a lead II ECG configuration. Twenty-minute "resting" control rhythm strips were recorded for all personnel. Each operative procedure was divided into four separate events and logged for anaesthetists (A1–4) and surgeons (S1–4): A1/S1 = induction of anaesthesia/scrub up; A2/S2 = maintenance of anaesthesia/skin incision and peroperative phase; A3/S3 = reversal of anaesthesia/unscrubbing; A4/S4 = 15-min interval in recovery area. Results were expressed as mean ± SEM and analysed for statistical significance using the Wilcoxon rank sum and signed rank tests where appropriate. $P < 0.05$ was considered statistically significant.

A significant increase in heart rate from control values was noted in both groups on induction of anaesthesia ($P < 0.01$) (fig. 2). In the surgical group the heart rate increase persisted throughout the procedure, while a return to baseline values during the peroperative phase was noted in the anaesthetic group. The heart rate increase was significantly greater on induction among anaesthetists compared with surgeons. There was no significant increase in heart rate during reversal or emergence from anaesthesia. A significantly greater increase in heart rate occurred during induction and surgical incision of

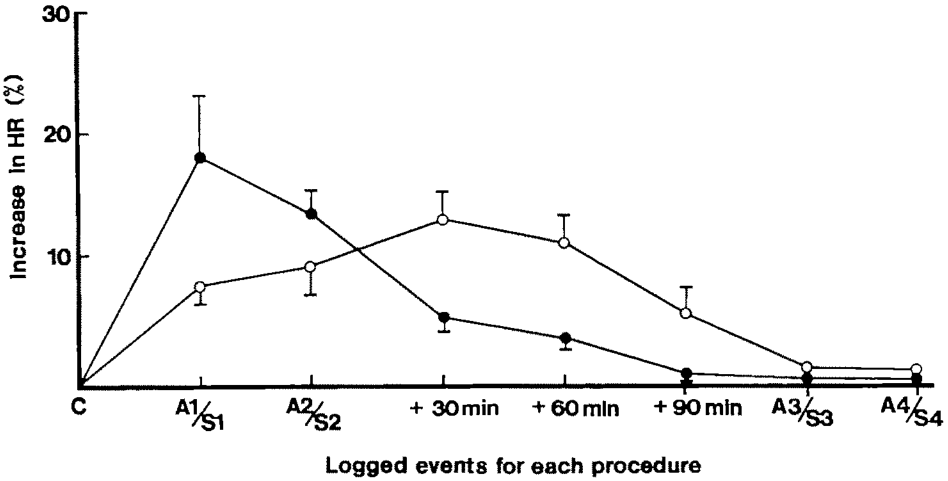

FIG. 2 Mean changes in heart rate throughout the day: lagged events for each procedure. ● = Anaesthetists; ○ = surgeons.

the first case of the day compared with the remaining patients (29.4% and 16% respectively, compared with 19% and 8%; $P < 0.01$). There was no correlation between maximum increase in heart rate and years experience in either group. Occasional premature ventricular contractions were noted in one individual.

Both anaesthetists and surgeons showed an increase in heart rate on induction of anaesthesia/skin incision. This persisted throughout the procedure in the surgical group only. Unlike previous studies (Harder, 1985) no tachycardia was observed at the reversal of anaesthesia and no association was observed between anaesthetist/operator stress and years experience.

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HEAT PRODUCTION AND ENERGY EXPENDITURE FOLLOWING SURGERY

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FACILITATION AND INHIBITION BY ATROPINE AND MUSCARINIC AGONISTS OF NEUROMUSCULAR TRANSMISSION AT THE RAT NEUROMUSCULAR JUNCTION

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The hypothesis of a local feedback regulation of acetylcholine (ACh) release in central nervous system and peripheral smooth muscle is well-established (Bourdois et al., 1974; Kilbinger, 1977). However, at the neuromuscular junction, the presence of an inhibitory presynaptic mechanism of ACh release has not been established yet, and there is evidence for and against such a mechanism (Abbs and Joseph, 1981).

The aim of the present investigation was to study the neuromuscular effects of atropine and of the muscarinic agonists, oxotremorine, pilocarpine and muscarine, to see if they modulated neuromuscular transmission, by altering the twitch, tetanic, post-tetanic twitch responses (PTT) and post-tetanic twitch potentiation (PTP) at the rat neuromuscular junction.

The phrenic nerve (and the diaphragm) was stimulated at 0.2–100 Hz with 2–5 V (maximal) and 0.1–0.5 ms square pulse duration. The ACh released by tetanic nerve stimulation, at 50 Hz for 20 s, was collected and assayed on rat ileum in the presence of neostigmine or edrophonium 0.7 µmol litre^{-1}. Hemicholinium 1.1 µmol litre^{-1} was added to block the presynaptic release of ACh.

The results showed that atropine 0.001–10 µmol litre^{-1}, pilocarpine 0.051–51.3 µmol litre^{-1}, muscarine 0.071–71.3 µmol litre^{-1} enhanced, whereas oxotremorine 0.006–60 µmol litre^{-1} reduced, the amplitudes of the indirectly-elicited twitch, tetanic and post-tetanic twitch responses (PTT). The PTP values were increased. The maximum potentiation or depression of the responses occurred with atropine 1 µmol litre^{-1}, oxotremorine 6 µmol litre^{-1}, pilocarpine 20 µmol litre^{-1} and muscarine 35 µmol litre^{-1}.

The results obtained with atropine 1 µmol litre^{-1} are shown in table V. Atropine 0.1 µmol litre^{-1}, pilocarpine 0.513 µmol litre^{-1}, muscarine 0.713 µmol litre^{-1} increased, whereas oxotremorine 0.6 µmol litre^{-1} decreased the contractions produced in the rat ileum, in response to tetanic stimulation at 50 Hz of rat phrenic nerve, by 63.6±2.1%, 36.4±1.3%, 27.3±1.1% and 45.5±4.2%, respectively (means±SEM; $n = 6$; $P < 0.001$).

TABLE V. *Effect of atropine 1 µmol litre^{-1}, on twitch (0.2 Hz), tetanic (50 Hz), post-tetanic twitch (0.2 Hz), and post-tetanic twitch potentiation (PTP) at the rat neuromuscular junction* (n = 6). *Mean values (mm)±SEM*

	(1) Twitch	(2) Tetanus	(3) PTT	PTP [(3–1)/ 1 × 100]
Control	14.0±0.6	42.7±1.8	16.9±0.5	20.7±1.6
Atropine	18.7±0.9	56.5±3.5	25.3±1.6	35.0±2.7
% Change	34.2±3.2	32.7±1.1	49.7±2.7	69.0±4.1
P	< 0.02	< 0.02	< 0.02	< 0.01

The different effects of muscarinic agonists used, with respect to atropine, suggested that (a) different muscarinic receptors may be present at the rat neuromuscular junction, and (b) activation of these receptors would result in modulation of neuromuscular transmission via both inhibitory and excitatory presynaptic mechanisms.

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ONSET AND DURATION OF PARALYSIS AFTER ATRACURIUM AND VECURONIUM GIVEN IN DIVIDED DOSES

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It has been shown previously that the onset of action of agents like alcuronium and pancuronium can be accelerated by administering them in divided doses, that is, a small "priming" dose being administered a few minutes before the main dose (Doherty et al., 1985; Black et al., 1986). In this study we have assessed the onset and recovery of neuromuscular blockade, following administration of atracurium and vecuronium in divided doses and compared these when the drugs were given as a single bolus dose.

Forty adult patients were included in the study after obtaining their informed consent and approval from the regional ethics committee. Premedication consisted of oral diazepam. Anaesthesia was induced with thiopentone and maintained with nitrous oxide in oxygen and fentanyl 4–5 μg kg^{-1} i.v. Following induction of anaesthesia, the ulnar nerve was stimulated percutaneously at the wrist with supramaximal stimuli of 0.2 ms duration at 0.1 Hz. The resultant force of thumb adduction was measured and recorded.

The control twitch height was allowed to stabilize for about 10 min. The patients were then allocated randomly to receive atracurium 0.5 mg kg^{-1} or vecuronium 0.1 mg kg^{-1} in single or in divided doses. The smaller priming dose was 10% of these doses (atracurium 50 μg kg^{-1} or vecuronium 10 μg kg^{-1}) and was administered 4 min before the remainder of the main dose. Selection of this priming dose and time was based on our previous studies of patient acceptability. Those receiving the relaxants in a single dose received an inert substance instead of the priming dose. The percent depression in twitch height with the priming dose, and the time to onset of block and duration to 25% recovery of the twitch height following the main dose were recorded.

Our results (table VI) showed no significant difference in either the onset of action or the time taken to 25% recovery of the twitch height when these were compared for each of the two relaxants between the single dose and the divided dose groups.

TABLE VI. *Onset of action and time to 25% recovery (R_{25}) (mean ± SD)*

	Primed group	Control group
Atracurium		
Onset (s)	142.0 ± 51.38	160.0 ± 54.36
Time to R_{25} (min)	38.8 ± 3.76	45.3 ± 11.33
Vecuronium		
Onset (s)	172.7 ± 41.83	166.4 ± 32.07
Time to R_{25} (min)	29.1 ± 7.41	34.8 ± 9.27

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FACTORS INFLUENCING EVOKED-REVERSAL OF NEUROMUSCULAR BLOCKADE

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Evoked reversal of neuromuscular blockade is known to depend on the degree of paralysis present when reversal is attempted and also on the anticholinesterase used and the dose in which it is administered (Rupp et al., 1986). In this study we have examined to what extent the ability to reverse a specific degree of block (T1 = 10% of control T1) is influenced by the neuromuscular blocking agent initially administered (pancuronium or vecuronium). As train-of-four (TOF) ratios of both 0.5 and 0.7 have previously been used to denote "adequate reversal" we were also interested to see whether the use of these different end-points influenced our results and conclusions.

After ethics approval, 17 adult patients, ASA class I and II, scheduled to undergo elective surgery requiring the use of neuromuscular blocking drugs, were studied. Electromyographic monitoring utilized the ulnar nerve at the wrist and the hypothenar muscles for positioning of the stimulating and recording electrodes. The train-of-four pattern of stimulation was used with supramaximal 0.1-ms square wave impulses. Anaesthesia was induced with sodium thiopentone 4–6 mg kg^{-1} and fentanyl 1 μg kg^{-1}. Control readings were obtained, then $ED_{95} \times 1.5$ doses of vecuronium (0.08 mg kg^{-1}) or pancuronium (0.1 mg kg^{-1}) were given as a bolus. Maintenance of anaesthesia was with oxygen in nitrous oxide 1:2 and 0.5% inspired halothane. A complete record of twitch height was obtained throughout. When the height of the first twitch in the train (T1) reached 10% of control, edrophonium 1.0 mg kg^{-1} and atropine 0.01 mg kg^{-1} were given. Comparisons were made between the neuromuscular blockers, of the time to achieve a TOF ratio of 0.5 and 0.7. Statistical analysis utilized Wilcoxon's Rank Sum test. Results are shown in table VII.

TABLE VII. *Results (mean values ± SD)*

	Vecuronium	Pancuronium	P
n	9	8	—
Age (yr)	31 (15)	57 (16)	
Weight (kg)	64 (8)	61 (9)	
Time to achieve TOF ratio 0.5 (min)	2.8 (1.5)	1.5 (1.0)	< 0.05
Time to achieve TOF ratio 0.7 (min)	9 (3)	36 (25)	< 0.01

Three patients, all of whom had been given pancuronium, required a supplementary dose of edrophonium to achieve a TOF value of 0.7.

To conclude, we have shown that the ability to reverse a specific degree of neuromuscular block (a T1 of 10% of control in this study) may be markedly influenced by the blocking agent which was originally administered. In addition we have shown that the precise end-point used to define "adequate reversal" influences the interpretation of the results. Reversal was reliable and rapid using edrophonium for both vecuronium- and pancuronium-induced blocks if a TOF ratio of 0.5 was the required end-point. However, using a TOF ratio of 0.7, reversal of vecuronium-induced block was reasonably rapid (9 min), but markedly prolonged if the blockade was produced by pancuronium (36 min).

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AN AUTOMATED METHOD FOR ANALYSIS OF VENTILATORY RATE AFTER OPERATION

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In patients after operation, ventilatory rate is often used clinically to assess the effects of opioid analgesics, but its reliability in this regard is not established. To obtain more information about the rate of ventilation and its variation in these circumstances, we detected ventilatory movements by transthoracic impedance, and recorded this signal for up to 24 h after operation.

Two electrodes were placed, one on each side of the chest, at the 6th intercostal space in the mid axillary line and used to pass a constant current of 100 kHz, 1 mA, and sense the resultant voltage. Chest movement typically resulted in a 1-ohm impedance change. The resultant voltage changes were recorded along with ECG from the same electrodes on a second channel using a miniature 24-h recorder as is commonly used for ambulatory ECG recording. Analysis of the signal for breath-to-breath intervals was carried out at 120 times real time using a specially developed hybrid computer, to obtain frequency histograms for any chosen epoch.

Thirty patients who received morphine continuously i.v. (at about 1 mg kg^{-1}/24 h) for pain relief after abdominal surgery were studied. In these patients, a signal that could be analysed was obtained for 73 ± 22% (mean ± SD) of the recording time. Ventilation rates and the range of breath-to-breath intervals varied considerably. For example, when the modal value of the period of ventilation was 2.2 s, the 95% percentile was at 2.6 s, but when the modal period increased to 4 s, the 95% percentile increased to 6.8 s.

The device is simple to apply and robust in use, needing no attention while in place, and should be helpful in the investigation of opioid analgesic effects in the postoperative period.

FACTORS INFLUENCING ATRACURIUM-INDUCED CUTANEOUS REACTIONS

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Atracurium is known to have a histamine-releasing potential (Barnes et al., 1984) producing histaminoid cutaneous reactions and, rarely, hypotension and bronchospasm (Siler, Mager and Wyche, 1985). Precipitation between alkaline thiopentone (pH 10.5) and acid atracurium (pH 3.5) has been suggested as a cause of cutaneous reactions (Fox, 1984) and the recommended method of administration involves either the use of a fast-flowing i.v. infusion or flushing of a winged i.v. needle with isotonic saline between the administration of thiopentone and atracurium.

A randomized clinical trial was designed to investigate some of the factors which might influence the occurrence of cutaneous reactions. Patients in ASA groups I or II, undergoing elective surgery, were allocated at random to one of the groups below. Group 1 received the drugs into a fast-flowing i.v. infusion, group 2 into a winged i.v. needle with flushing as described above and groups 3 and 4 into a winged i.v. needle without flushing, located either in the antecubital fossa (group 3) or in the dorsum of the hand (group 4). Anaesthesia was induced with thiopentone 5 mg kg^{-1} given over 20 s. Cutaneous reactions were noted, as was hypotension or bronchospasm if present.

The possibility of Hofmann elimination beginning in the ampoule on warming to ambient temperature was investigated by keeping the drug at room temperature for 2–3 weeks before administration (group 5).

A separate group of patients with a known history of drug allergy (group 6) was studied by the method of group 1, as was a further group composed of elderly patients (> 70 yr; group 7). The results are summarized in table VIII.

TABLE VIII. *Findings in the various groups of patients receiving thiopentone and atracurium by one of the regimens described in the text*

Group	*n*	Cutaneous reactions (%)	Hypotension (> 40 mm Hg) (%)
1	30	63	13
2	30	67	3
3	30	60	17
4	30	70	7
5	30	63	20
6	25	72	12
7	25	8	64

There was a high incidence of cutaneous histaminoid reactions to atracurium which were of short duration and rarely associated with other signs of histamine release. The reactions did not appear to be related to the method of administration or lack of refrigeration, and they were very uncommon in elderly patients.

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COMPARISON OF FADE IN TRAIN-OF-FOUR DURING ONSET OF NON-DEPOLARIZING NEUROMUSCULAR BLOCK

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SYMPATHOADRENAL RESPONSES TO TRACHEAL INTUBATION AFTER THIOPENTONE OR PROPOFOL

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This study compared the cardiovascular and catecholamine responses to tracheal intubation in patients in whom anaesthesia was induced with either thiopentone or propofol. Healthy patients (ASA I or II) age 16–40 yr undergoing gynaecological procedures were included in the study.

Oral premedication with diazepam 10 mg was given

60–90 min before surgery. At induction, fentanyl 100 µg was given i.v. followed 1 min later by the induction agent (thiopentone 4–5 mg kg^{-1} or propofol 2–2 5 mg kg^{-1} randomly allocated). Muscle paralysis was achieved using vecuronium 0.1 mg kg^{-1}. The patients' lungs were ventilated using a Bain circuit with an appropriate fresh gas flow to achieve normocapnia. Intubation was carried out at 2 min and ventilation at normocapnia was continued with 67% nitrous oxide in oxygen throughout the study period.

Heart rate and systolic and diastolic arterial pressures were measured using a semi-automated sphygmomanometer. Venous blood samples were taken from an indwelling cannula in the antecubital fossa contralateral to the injection site for determination of plasma noradrenaline and adrenaline concentrations by HPLC. Sample times were: baseline (pre-induction in the anaesthetic room); 1 min after induction and 1, 3 and 5 min after intubation.

Results from 14 patients in the thiopentone group and 17 patients in the propofol group are presented. There was an increase in heart rate of 30% at 1 min and 20% at 3 min after intubation in comparison with the baseline in the thiopentone group, and in both groups there was an increase in heart rate of between 10% and 20% 1 min after intubation in comparison with post-induction values. No difference was observed between the groups.

Both drugs produced a decrease in systolic arterial pressure after induction in comparison with baseline and this decrease was greater in the propofol group (30%) in comparison with that in the thiopentone group (12%). At 3 and 5 min after intubation, systolic arterial pressure remained lower than baseline in the propofol group, and was significantly lower than the equivalent values in the thiopentone group.

There was an increase in systolic arterial pressure after intubation in both groups of 27%, compared with the immediate pre-intubation values. The increase in systolic arterial pressure at intubation was associated with an increase in plasma noradrenaline concentration 1 min after intubation in the thiopentone group, but not in the propofol group. No changes either within or between the groups were observed in respect of adrenaline concentrations.

ATRACURIUM COMBINED WITH ALCURONIUM

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Anaesthetists sometimes combine alcuronium and atracurium to intubate the trachea, and sometimes supplement alcuronium with atracurium to maintain paralysis. We have studied neuromuscular transmission in 18 patients undergoing prolonged (pancreatic, oesophago–gastric or abdomino–perineal) procedures lasting 4–6 h, to look for possible interactions between the two drugs. All patients received atracurium alone to facilitate tracheal intubation and the study concerns the effects of supplements. We used a Grass FT 03 force transducer on adductor pollicis in the first six patients and a Datex Relaxograph on the first dorsal interosseous in the last 12. In nine "control" patients we studied the duration of action of successive doses of atracurium (either 5 or 10 mg). In nine "test" patients we compared the duration of action before and after a single dose of alcuronium 7.5–10 mg. For each patient, the incremental doses of neuromuscular blocking drug were given when the T1 response returned to a fixed percentage of the control response, chosen for that patient depending on the individual requirements for adequate surgical paralysis. The intervals between requirements provided the index of duration of action for comparisons within each patient.

Atracurium is regarded as non-cumulative, in that there is no progressive increase in duration of action at the doses used (Payne and Hughes, 1981). In our nine control patient, there were small variations in duration of effect around a perceptibly increasing trend, doses given in the 3–4 h after the start lasting 1–1.3 times longer than doses given between 1 and 2 h. This was not obviously related to a decrease in oesophageal temperature, although there may have been a shrinkage of the notional "core" at "core" temperature.

In the nine test patients in whom we compared the duration before and after alcuronium, the pre-alcuronium doses were given in the 1–2 h after the start, and the post-alcuronium doses in the 3–5 h after the start. The post-alcuronium doses lasted between 1.5 and 2.5 times longer than the pre-alcuronium doses. This effect did not depend on the dose of atracurium, or the percentage T1 which had been chosen as the indication for giving the increments. In six patients in whom two or more post-alcuronium doses were given, the second and later doses were prolonged as much as the first. By contrast, Kay and others (1986) found that, after pancuronium, a succession of doses of vecuronium gave progressively decreasing durations of action, until the presumed residual effects of the pancuronium had worn off.

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MONITORING OF MECHANICAL TWITCH IN THE DIAPHRAGM DURING ANAESTHESIA

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The function of the muscles of ventilation is usually assessed indirectly. However, direct assessment of diaphragmatic contraction is possible by measurement of the pressure gradient across it (P_{di}); this can be achieved non-volitionally after stimulation of the phrenic nerve to produce an objective measurement of diaphragm strength. In anaesthetic practice, assessment of onset and recovery from the effect of neuromuscular blocking drugs is usually deduced indirectly from ventilation or by monitoring non-ventilatory skeletal muscle after stimulation of its motor nerve. We have used a non-volitional technique to measure ventilatory muscle strength during anaesthesia with conventional doses of neuromuscular blocking drugs.

Unilateral phrenic nerve stimulation was performed percutaneously in the neck using a programmable nerve stimulator and hand-held stimulating electrode with the indifferent electrode on the sternum. The stimulating current was adjustable to a maximum of 35 mA into a 5-kΩ load and stimulus width in most cases was 100 µs, although in one case 200 µs was necessary to achieve supramaximal stimulation. Preliminary investigation was undertaken to ensure that supramaximal stimulation was possible and to test the ability to stimulate the phrenic nerve consistently for long periods. Anaesthesia was induced with thiopentone, and intubation of the trachea performed under suxamethonium; the patients then breathed halothane supplemented with i.v. analgesics as appropriate. Air-filled balloon catheter systems were used to measure oesophageal (P_{oes}) and gastric (P_{gas}) pressures, an abdominal strain gauge (ASG) was used to monitor diaphragmatic configuration, and a myograph was attached to one forearm to record adductor pollicis twitch. All four traces (P_{oes}, P_{gas}, ASG and myograph) were recorded on a six-channel pen recorder and P_{di}, obtained by electronic subtraction ($P_{gas} - P_{oes}$), was simultaneously displayed on a fifth channel.

Subsequently, we studied six healthy patients (four men; age range 21–64 yr) undergoing surgery for varicose veins. After administration of a single dose of atracurium 0.5 mg kg^{-1}, supramaximal stimulation at 1 Hz was used to monitor the disappearance of diaphragm and adductor pollicis twitch. Spontaneous return of neuromuscular function was observed using train-of-four stimulation in both the phrenic and ulnar nerves. Onset of diaphragmatic block occurred at a mean of 40.7 s (SD 12.1) and that in the adductor pollicis at 67.3 s (SD 27.3). Signs of return of neuromuscular function were seen at 1390 s (SD 433) and 1884.7 s (SD 448.3), respectively. In every case, blockade and onset of recovery in the hand was preceded by that in the diaphragm.

FREQUENCY DEPENDENCE OF THE MECHANICAL RESPONSE OF THE VENTILATORY SYSTEM TO HIGH FREQUENCY VENTILATION

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When high frequency jet ventilation (HFJV) is applied to a patient, gas exchange may be influenced by his mechanical response to the ventilator. This response has been considered conventionally to be dependent on the compliance of the lungs and the resistance to gas flow in the airways. At higher ventilation frequencies as in HFJV, the factor of inertance has to be taken into account. The model then becomes analogous to a simple mechanical oscillator (Lin and Smith, 1986) in which mechanical resonance could be excited by the ventilator, provided that (i) the appropriate driving frequency is applied, and (ii) the damping in the system is below a certain value.

As the driving frequency approaches resonant frequency, f_0, the gain of the system (defined by the ratio output to input) reaches a maximum. Concurrently, phase shift of $\pi/2$ rad takes place between the input and output to bring them into phase with each other at f_0. The output will also be dependent on the mechanical damping in the system. When the damping is great enough the output will not peak at f_0 (Kreyszig, 1965).

This study was undertaken to examine the mechanical response of the ventilatory system in pigs to the application of HFJV. Six pigs of varying body weights were used and were anaesthetized, intubated and established on HFJV from a prototype Penlon Bromsgrove jet ventilator. The input to their ventilatory systems was taken as the baseline to peak airway pressure measured in the endotracheal tube. A chest strain gauge recorded excursions of the chest wall as the mechanical output of the system. The phase relationship between input and output was also measured. Routine cardiovascular monitoring was applied to ensure stability during measurements. Measurements were then made as the ventilation frequency was varied over a range of 1–10 Hz.

The results showed that the gain in the six pigs varied with ventilation frequency and demonstrated a maximum at a given frequency. The frequency at which maximum gain occurred was different for each pig. The occurrence of the maximum gain was accompanied by a phase shift between the input and output of approximately $\pi/2$ rad.

The inferences from these results are that mechanical resonance can be excited at the ventilation frequencies attainable during HFJV, the damping in a healthy ventilation system is low enough to allow peaking of the chest wall excursions, and finally that the resonant frequency may be related to body weight (table IX).

TABLE IX. *Results*

Pig	Body wt (kg)	Freq. for max. gain (Hz)	Freq. for phase shift = $\pi/2$ (Hz)
1	17	8.3	7.8
2	19	6.0	6.6
3	35	5.1	4.75
4	35.5	4.9	4.8
5	42	4.46	4.65
6	62	3.5	3.9

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ISOFLURANE PREVENTS EEG DEPRESSION BY TRIMETAPHAN-INDUCED HYPOTENSION IN MAN

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We have demonstrated previously in man that, at equivalent levels of arterial hypotension, the EEG is significantly more depressed by trimetaphan (TMP) than by sodium nitroprusside (Thomas et al., 1985). This confirmed earlier work in cats by Ishikawa and McDowall (1981) who also demonstrated that declining EEG "power" correlated with decreasing cerebral blood flow during hypotension. It appears that isoflurane may protect the brain by its effects on cortical electrical activity and cerebral metabolism in experimental models of incomplete global cerebral ischaemia (Newberg and Michenfelder, 1983). We now report an investigation of whether this effect can be seen during induced hypotension in man.

A preliminary study delineated the effects of isoflurane (12 patients) and halothane (11 patients) without hypotension on the EEG (Cerebral Function Analysing Monitor, digital output of five amplitude and 10 frequency variables) together with brainstem auditory evoked potentials. The quantitated changes in the EEG at steady state 1% end-tidal isoflurane at normocapnia and normotension were not significantly different from those changes seen in 10 similar patients before the induction of hypotension with TMP. Arterial pressure was then reduced to values comparable to those of Thomas and others (1985) using similar general anaesthetic and monitoring procedures but substituting isoflurane for halothane. In the previous study (Thomas et al., 1985) hypotension induced by TMP on a background of halothane led to decreases in EEG voltage in all 10 patients studied (6–53%, mean 25.5 ± 11%). In contrast in the 10 patients receiving isoflurane, only small decreases in EEG voltage were seen and were confined to six patients, with a small increase (0.5–2.9%, mean 1.4 ± 1%, $n = 4$) being seen in the remaining four. The range of decreases in EEG voltage was (1.1–3.8%, mean 2.1 ± 0.5%, $n = 6$). In no patient was the change in EEG voltage, as compared with prehypotensive values, significant and in no patient was it significantly correlated with acutely decreasing arterial pressure values.

These results suggest that isoflurane, at a steady concentration insufficient to produce burst suppression in the EEG, is capable of preventing or reducing the adverse effects on the EEG of TMP-induced hypotension in man.

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CORRESPONDENCE

A VENTILATOR FOR CARBON DIOXIDE LASER BRONCHOSCOPY

Sir,—In their article "A ventilator for carbon dioxide laser bronchoscopy", Drs Paes, Conacher and Snellgrove (1986) quoted us, but erroneously.

We have reported the use of "high frequency jet ventilation", not that of "high frequency positive pressure ventilation". This was clearly stated in our articles (Vourc'h et al., 1983a, b); we have used a high feeding pressure and ventilation rates up to 300 b.p.m. Furthermore, our device was inducing air entrainment. Those three features are characteristic of high frequency jet ventilation.

The authors warn against the risk of air trapping when the telescope is inserted to the bronchoscope. Our experimental study (Fischler et al., 1985) shows that there is, indeed, an increase in lung volume, but that it is minimal especially when the I:E ratio is kept low (0.25), as is the case in clinical practice. No case of pneumothorax has been recorded since we have been using HFJV in bronchial surgery.

The bronchoscope described by the authors is the replica of that previously described by us in the *British Journal of Anaesthesia* (Vourc'h et al., 1980) and in *Thorax* (Toty et al., 1981) and the authors are using our own words to describe their bronchoscope.

G. Vourc'h
M. Fischler
Suresnes, France

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—— Tannières, M. L., Toty, L., and Personne, C. (1980). Anaesthetic management of tracheal surgery using the Nd YAG laser. *Br. J. Anaesth.*, 52, 993.

Sir,—Thank you for the opportunity of replying to the letter from Professor Vourc'h and Dr Fischler.

A transcribing error was made during preparation of our manuscript. High frequency positive pressure ventilation should have read high frequency jet ventilation. The text following this reference indicates that we were discussing jet ventilation. We do apologize for the error.

Jet ventilation is not as simple as Professor Vourc'h states in his letter, particularly in the presence of tracheobronchial stenosis. Air entrainment is reduced in the presence of various conditions such as:

(a) high airway resistance and low pulmonary compliance (Jardine, Harrison and Healy, 1975);

(b) obstruction of the operator end of the bronchoscope with the insertion of telescopes, eye pieces and other instruments (Sanders, 1967; Fischler et al., 1985);

(c) the oblique angle of the jet conduit in relation to the bronchoscope of the modified STORZ bronchoscope that is used by Professor Vourc'h's team;

(d) probable reduced entrainment as a result of the lower velocity in using a 2.5-mm wide tube for the jet.

All these conditions may relate to jet ventilation for laser surgery in the airway.

In their articles (Vourc'h et al., 1983a, b), Professor Vourc'h and his colleagues measured blood-gas tensions before anaesthesia, 10 min after manual jet ventilation and then 10 min after instituting high frequency jet ventilation. Their results show a decrease in Pa_{CO_2} after manual jet ventilation followed by an increase in Pa_{CO_2} in each step after instituting high frequency jet ventilation. As laser procedures (both carbon dioxide and Nd Yag) take considerably longer than 10 min, one must assume that the Pa_{CO_2} would have increased to much higher values as we have experienced in our practice.

In respect of their second point of contention, our article (Paes, Conaches and Snellgrove, 1986) stated "Introduction of the fibrebronchoscope, which carries the laser fibre, to the lumen of the rigid bronchoscope will cause a decrease in entrained volume and a decrease in the elimination of carbon dioxide. In patients with airway tumours, one must be aware of the risk of gas trapping with this technique. Deceasing the inspiratory/expiratory ratio may minimize this problem". If the correspondents read our article carefully, they would find that they have expressed similar views in their numerous articles.

The description of their bronchoscope varies from one article to another: "a 16-gauge brass tube was therefore welded to the inside of the bronchoscope, opening at the tip" (Vourc'h et al., 1980); "therefore a 16-gauge brass tube was welded on the side of the bronchoscope opening at the tip, and within the lumen to avoid damage to the mucosa by the jet of compressed gases" (Toty et al., 1981); "a rigid Storz bronchoscope (internal diameter 10 mm) was modified by welding a 2.5 mm brass tube on the outer side, the opening of the tube lying obliquely 8 cm from the tip of the bronchoscope" (Fischler et al., 1985).

The bronchoscope we use is supplied by Wolf for carbon dioxide laser bronchoscopy. Our description of it is confined to that part of the bronchoscope which is relevant to our ventilation technique. The Wolf CO_2 laser bronchoscope is a modification of their conventional one and differs "by the addition of a narrow conduit 2 mm in diameter extending along the whole length of the outer wall and ending within the bronchoscope 1 cm from the tip. This channel was designed for smoke extraction. Operation of the laser bronchoscope ventilator converts this channel into a conduit for ventilation as well as smoke extraction".

In Sanders' original publication on jet ventilation, he mentions the availability of bronchoscopes with channels or ducts built into the side of the instrument for the purpose of gas delivery, 10 years before its publication. Sir, neither Professor Vourc'h nor we are describing anything original in relation to bronchoscopes.

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I. D. CONACHER
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THE GRASS FT 03 TRANSDUCER SHOULD NOT BE USED FOR HUMAN EXPERIMENTS

Sir,—In their recent report on priming with alcuronium, Black and colleagues (1986) described the use of Grass FT 03 transducer for measurement of the force of the adductor pollicis in response to ulnar nerve stimulation in adults. The FT 03 transducer is rated a 2-kg maximum (Grass Instruments, Quincy, MA, U.S.A.). Freund and Merati (1973) have noted that this transducer may be a "source of errors in assessing neuromuscular blockade" since it is designed for small animal experiments. Instead, they note, the model FT 10, rated at 10 kg should be used.

Some of the measurements showing no fractional twitch depression in the study of Black and colleagues (1986) may be the result of an overloaded transducer. Thus use of the FT 10 transducer may show lower latency times.

M. SOSIS
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Sir,—Dr Sosis has made a valid point, but I do not think transducer overload was responsible for failure to show twitch depression with our priming doses or for artificially long latencies. The FT 03 was always able to register forces considerably greater than the unparalysed single twitch, if we applied a tetanus or if we applied graded extra pressure on top of the patient's thumb. It is important to check that any transducer is being used within its limitations rather than abandon it altogether—especially if it is all you have. We think we now have a very good reason for abandoning our FT 03—namely, a Datex Relaxograph! Although it has its own set of very different problems, our observations with it have been quite consistent with those we reported in respect of the effects of priming doses and latencies of onset.

A. M. S. BLACK
P. HUTTON
T. CLUTTON-BROCK
Bristol

QUANTIFICATION OF SYMPATHETIC BLOCKADE BY THERMOGRAPHY

Sir,—In their paper McCollum and colleagues (1985) discussed the use of thermography in the assessment of the efficacy of sympathetic blockade and in the prediction of the need to perform sympathetic blocks in certain patients (diabetics). This use of thermography in the qualitative assessment of sympathetic blockade is not new (Diaz, 1976). One of the major problems in the assessment is, however, that many other factors (smoking, drugs, eating and ambient temperature) have a large influence on skin blood flow when measured by skin temperature.

In this department I have been evaluating aspects of sympathetic blockade using contact thermography ("Nova Therm", Novamedix Ltd). Early in this study I was concerned by the "corruption" of images by other factors and looked for a method of improving the accuracy of the technique.

Using a plethysmographic system, Glynn and colleagues (1982) had shown that skin blood flow and, in particular, the response of blood flow to the proximal application of ice, was the most specific measure of sympathetic activity. On the base of these observations I started to quantify sympathetic tone and sympathetic blockade by a thermographic ice response test. Thermography is performed after the application of ice to either the proximal limb or the trunk. The response is reproducible and sympathetic blockade is evident from a failure of vasoconstriction with ice. This has been of value in clinical work as well as as a research tool.

In a study of sympathetic tone and blockade, it is important to quantify the response to stimulation. Thermography on its own does not satisfy this criterion because the image is corrupted by extraneous factors. The "thermography ice response" does fulfil this requirement and allows accurate analysis of sympathetic tone.

P. A. J. Hardy
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Sir,—We are grateful for the opportunity to respond to Dr Hardy's comments.

First, we do not doubt that others have used thermography in a qualitative way to assess the effects of sympathetic blockade. However, the paper by Diaz (1976) refers to observations on one subject, a case study in effect, and could hardly be considered definitive.

Second, our study was concerned primarily with the use of sympathetic blockade in ischaemic feet rather than in patients with adequate vasodilatory potential. In ischaemic limb conditions the magnitude of perfusion changes following sympathetic blockade may be greatly reduced. Further, impairment to the skin microcirculation may be unequally distributed around the foot, so it is important to visualize regional flow changes to determine the effectiveness of the blockade. As a consequence of our study, which has since been reinforced by additional data, it has become clear that patients with ischaemic rest pain should not have a sympathectomy if the ankle/arm pressure index is less than 0.35 or if the patients have evidence of a diabetic neuropathy.

Third, thermograms of ischaemic feet are much less susceptible to corruption by extraneous factors such as smoking, drinking and ambient temperatures in the range 20–26 °C because the normal autoregulatory mechanisms which continually adjust skin blood flow are severely impaired and the skin microcirculation is effectively under local metabolic control in response to a low arterial pressure. Additionally, the effect of any "corruption" can be more or less eliminated by making skin temperature comparisons with the contralateral limb.

It may be that there are specific problems associated with liquid crystal contact thermography as it differs substantially in both application and accuracy from high resolution infra-red imaging.

Finally, we were interested in Dr Hardy's attempts at quantifying the intensity of sympathetic activity by the application of ice to the proximal limb. Our theoretical and experimental studies have shown that a transient reflex vasoconstriction (less than 30 s) would be unlikely to reduce skin surface temperature by more than 0.2 °C. Liquid crystal thermography would not be sensitive enough to detect this change. It is possible that Dr Hardy is seeing a generalized thermoregulatory peripheral vasoconstriction leading to limb cooling. This cooling, which would not occur in sympathectomized limbs, would be observable by liquid crystal contact thermography.

We have recently used a laser doppler flowmeter (Periflux PF2) which, with its rapid response time, provides a more sensitive index of local vasoconstriction than that recorded thermally (Emslie-Smith et al., 1986).

V. A. Spence
P. T. McCollum
W. McRae
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S. B. Wilson
Dundee

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PRETREATMENT WITH RANITIDINE

Sir,—I have read the paper by Wilson and colleagues (1986) on the effect of ranitidine on the hypnotic action of single doses of midazolam, temazepam and zopiclone, and feel that further comment is required.

There is no reference within the paper regarding the randomization of treatments, without which, bias would be introduced. The addition of an extra 24 patients into the group given midazolam premedication would certainly introduce bias.

The use of three observers is a cause of concern in such a study. Any effect noted may well represent a difference between observers and not treatments if the observers were not equally represented within treatments.

The addition of patients to one part of a trial after examining the results is a procedure which contravenes accepted scientific and statistical principles. The only data which it is permissible to interpret are those from the original design—that is, in this case, 20 patients in each treatment group.

The data presented in this paper must be considered in the light of these comments, together with an earlier report of the same study (Dundee et al., 1985) in which it was reported that the influence of ranitidine on the hypnotic action of oral midazolam is small and probably of little importance, but may be clinically relevant only if large doses are given. Other studies (Klotz, Arvela and Rosenkranz, 1985; Greenblatt et al., 1986) have shown no interaction between midazolam and ranitidine.

Additionally, it is unworthy of a scientific publication to have excuses, explained at length, to rationalize why the study was not pursued to its logical scientific conclusion. Important studies of this type with direct clinical relevance should be carefully designed, completed and then reported.

D. J Wilkinson
London

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Sir,—I admit the omission of the word "randomized" from the methodology and apologize for this error. However, I would have hoped that we were a sufficiently reputable group of workers that it would be realized that this was a mistake.

Increasing the numbers in two series does *not* introduce bias provided, as we have stated, "neither patients nor observers knew the medication given". I was not involved in the observations or the anaesthesia, but I kept a constant watch on the findings and without the knowledge of my junior colleagues, withdrew temazepam and zopiclone after 120 observations, restricting the study thereafter to midazolam. With two operating lists per week containing one or two suitable patients, this had already taken about 1 year. Since most lecturers and research fellows have a 1-year contract, any alternative would have introduced a new group of observers.

The very exhaustive survey of our method of evaluation by Morrison, Hill and Dundee (1968) showed the fears of observer difference to be negligible. The alternative of one person making 120 or 144 observations is quite unacceptable because of the problem of boredom and inadvertent attempts at "breaking the code".

Your correspondent can have little contact with the real world of clinical research to consider lack of "money, availability of staff and time" as excuses for an incomplete study—they are facts of life. It he wants another, our hospital unit was due for closure.

With decreasing resources, one might well take a realistic look at some of the "sacred cows" in clinical research. This letter is a good example of them. The first 120 observations occupied about 1000 man-hours. It was not only good science, but good stewardship of resources (which include manpower) to complete the study as reported.

J. W. Dundee
Belfast

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BLOCKED EAR AFTER EXTRADURAL INJECTION

Sir,—Hardy (1986) reported three patients with hypoacusis after extradural injection. In fact they complained of a blocked ear (sensation of fullness or cotton wool). While hypoacusis is usually associated with subjective hearing difficulty and low tone hearing loss, these may be absent. Serial pure tone audiometry is needed to establish the hypoacusis.

Hardy noted that these symptoms of slight endolymphatic hydrops can occur after decreased CSF and perilymph pressures, but still claimed his patients' problems were caused by increased pressures. However, his findings are quite consistent with the more generally applicable low pressure theory. Note that:

(1) Symptoms occurred immediately after, rather than during, injection at a time CSF pressure is rapidly decreasing (Usubiaga, Wikinski and Usubiaga, 1967).

(2) Injection causes arterial pressure to decrease (Lund, 1971). Hydrops is associated with arterial hypo-, not hyper-, tension (Gordon, 1983).

(3) There may have been undetected dural puncture, with CSF leak or decompression.

(4) Two patients were young women. Injection CSF pressures are higher in older patients (Usubiaga, Wikinski and Usubiaga, 1967), while low pressure headaches are commoner in younger patients (Lund, 1971).

CSF hydrodynamics are complex and it is easy to make false assumptions. Thus it is generally considered that aqueduct stenosis is caused by hydrocephalus, even though the narrow lumen strongly suggests a centripetal pressure gradient with low pressures in parts of the CSF system (Gordon, 1984). There has long been confusion as to whether postspinal puncture headache is the result of increased or decreased CSF pressure (Lund, 1971). Aboulker (1919) claimed Menière's syndrome was the result of intracranial and labyrinthine hypertension and that symptoms (but not deafness) were relieved by decompression. However, instead of the expected jet of CSF at lumbar puncture, it often came out drop by drop or even a dribble. His explanation was that pressures vary at different parts of the CSF system.

There are more general reasons for discounting a causal increase in pressure. Hydrops symptoms do not occur in intracranial hypertension from space-occupying lesions, although vertigo may be a late brainstem symptom (Zulch, Mennel and Zimmermann, 1974). There is no aural analog of papilloedema or congestive inner ear (Kaaber and Zilstorff, 1978). Nor do they occur in pseudotumor cerebri, although a case of hydrops-type deafness has been reported (Sismanis et al., 1985). Significantly, they did not attribute this to increased perilymph pressure, despite immediate remission of deafness and tinnitus upon drainage of CSF, since the deafness also remitted during jugular vein compression, which increases CSF and perilymph pressures.

It is important to determine if high CSF pressure ever causes early hydrops symptoms, since otherwise they will be specific to CSF hypotension, unlike all the other symptoms which are common to CSF hyper- and hypotension (Frederiks, 1976). They would then be a simple and very useful clinical indicator of low pressure in lumbar puncture headache, overshunted hydrocephalus, spaceflight sickness, psychiatric disease, etc. Furthermore, the misleading high pressure theories of the causation of Menière's disease could be discarded. The way to settle the issue is to question patients carefully during CSF pressure measurements for all the symptoms of hydrops. The full early hydrops syndrome comprises a blocked ear, fluctuant low tone deafness or, on occasion, improved pure tone sensitivity, vertigo, tinnitus, audiosensitivity and lowered acoustic reflex thresholds (Gordon, 1986). The effect of posture should be noted, since low pressure symptoms should improve on lying down, while high pressure ones worsen.

Finally, idiosyncratic differences, in temporal bone anatomy or otological history perhaps, must predominate over general theoretical considerations, since side-effects occur in only a few patients, although hydrops symptoms are very easy to miss or misinterpret.

A. G. GORDON
London

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Sir,—Dr Gordon claims that the evidence I presented is consistent with his claimed description of an exclusive low pressure theory of "Hydrops syndrome" (Gordon, 1983)—a theory based on anecdotal evidence only and refuted in the same journal (Colman, 1983). If I take each of Gordon's points in turn, it is clear that there is no evidence to support a low pressure origin:

(1) The CSF pressure decrease described by Usubiaga, Wikinski and Usubiaga (1967) is that from a high pressure towards normal. These workers did not demonstrate any subnormal pressures and, in fact, noted increased residual pressures after injection. It has recently been shown that a similar increase in intracranial pressure occurs during extradural injection (Hilt, Gramm and Link, 1986) which may be prolonged in cases of reduced cerebrospinal compliance (Hardy, 1986).

(2) Spinal and extradural analgesia may be associated with a decrease in arterial pressure—well after the time period described. In the cases I described, arterial pressure monitoring showed no change after injection.

(3) Dural puncture in the presence of extradural injection of local anaesthetic would result in massive (total) spinal anaesthesia. This did not occur in the patients reported.

(4) The young patients described were pregnant women at term in labour. This is associated with increased intraspinal pressures (Messih, 1981).

(5) The patients were horizontal throughout which, as Dr Gordon notes, would minimize or negate any low pressure effect.

It would be interesting to know exactly on what experimental data Dr Gordon bases his low pressure theory. In the sources he quotes there is one clear description of "hydrops syndrome" associated with increased intracranial pressure which responded to CSF drainage (Sismanis et al., 1985).

Since my original letter I have noted both auditory and, in particular, vestibular disturbance in a patient *during* extradural injection of steroid–saline mixture in the treatment of low back pain. The 37-yr-old woman had a history of Menières disease, but was in remission. An extradural puncture was performed at L2–3 with the patient in a left lateral position. Injection of a solution of methylprednisolone 40 mg in 0.9% sodium chloride was performed at a rate of 4 ml min^{-1}. By the time 16 ml had been injected, the procedure had to be abandoned because of disabling waves of vertigo and the feeling of nausea. These symptoms persisted for about 5 min before gradually subsiding. Arterial pressure was stable throughout. The patient would not open her eyes during injection, so that it was not possible to check for nystagmus. After an uneventful recovery she described marked tinnitus and almost complete deafness during this episode. She also remarked that the symptoms were identical with but more severe than those she experienced with the Menières. In this patient, vestibular disturbance predominated although auditory disturbance was present also. The only change in association with these symptoms was a slow extradural injection, a procedure which is associated with *increased* spinal and intracranial pressures.

Do these symptoms matter? There are two reasons why these observations are important. To the anaesthetist these same symptoms may be caused by systemic local anaesthetic toxicity and not, as in this patient, a purely mechanical effect. To the otologist the mechanism is important, since there have been no studies of intracranial pressure in patients with VIII nerve diseases. The relationship between ICP and vestibular cochlear mechanisms would be worthy of further study

P. A. J. HARDY
Liverpool

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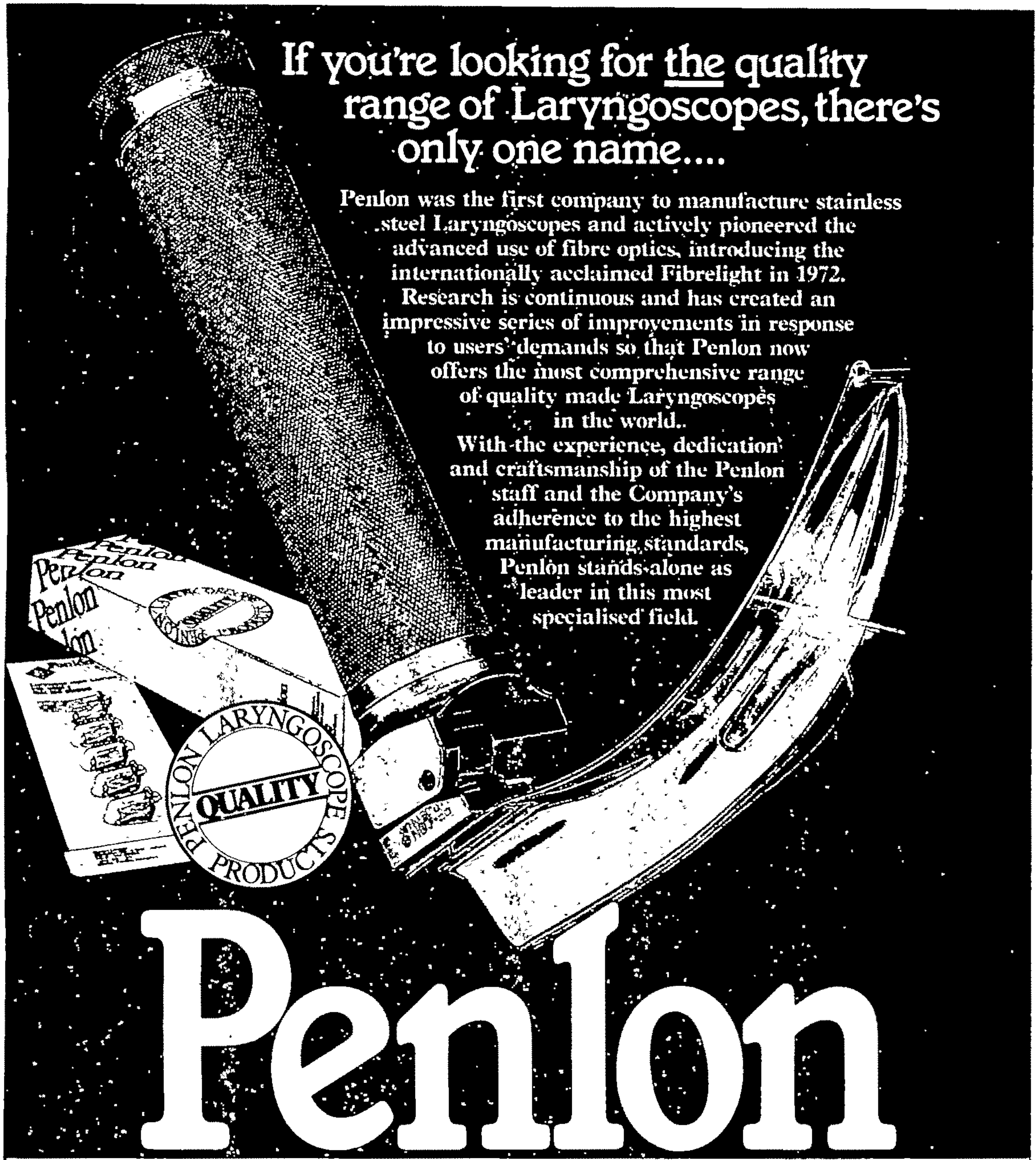

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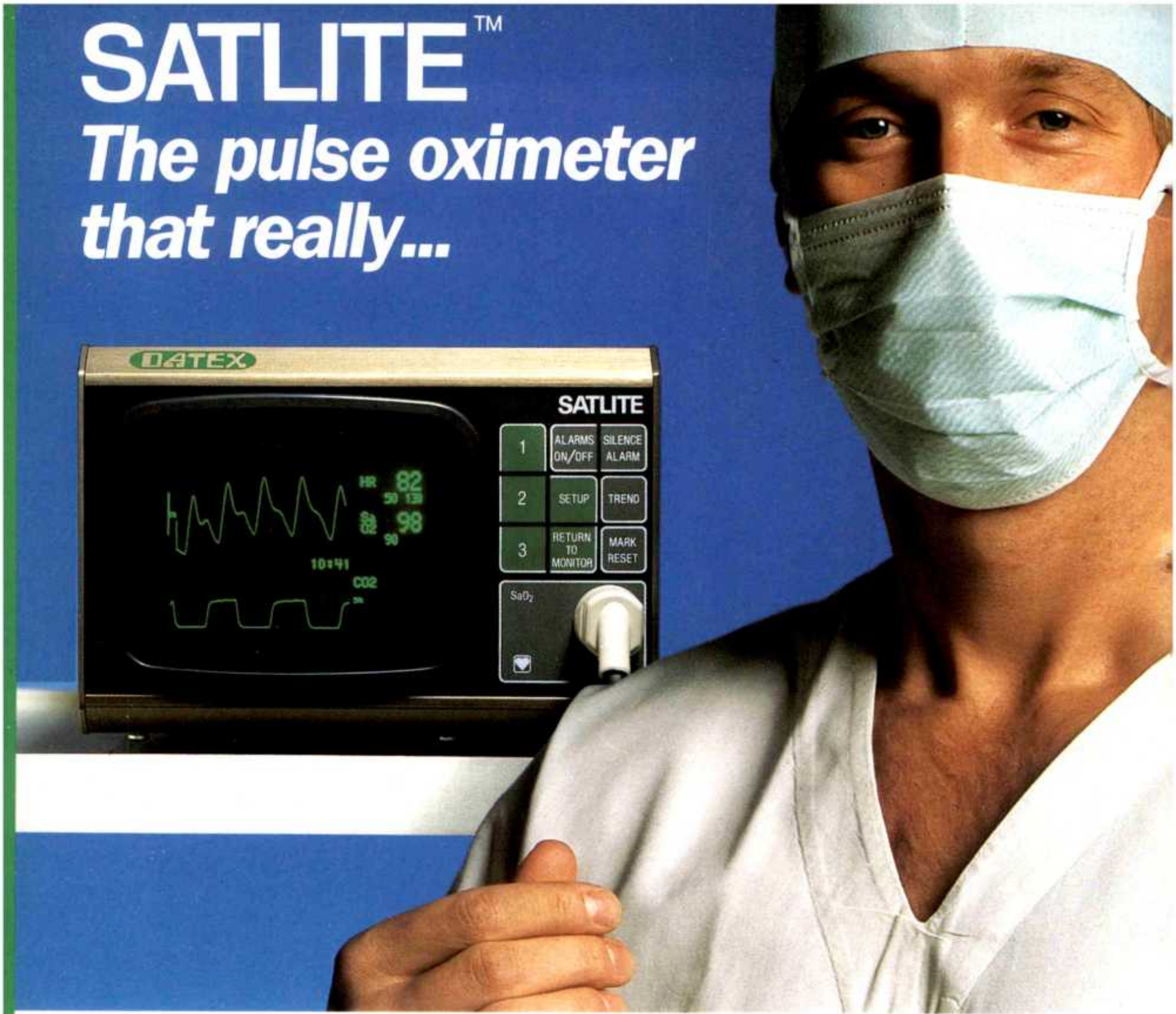

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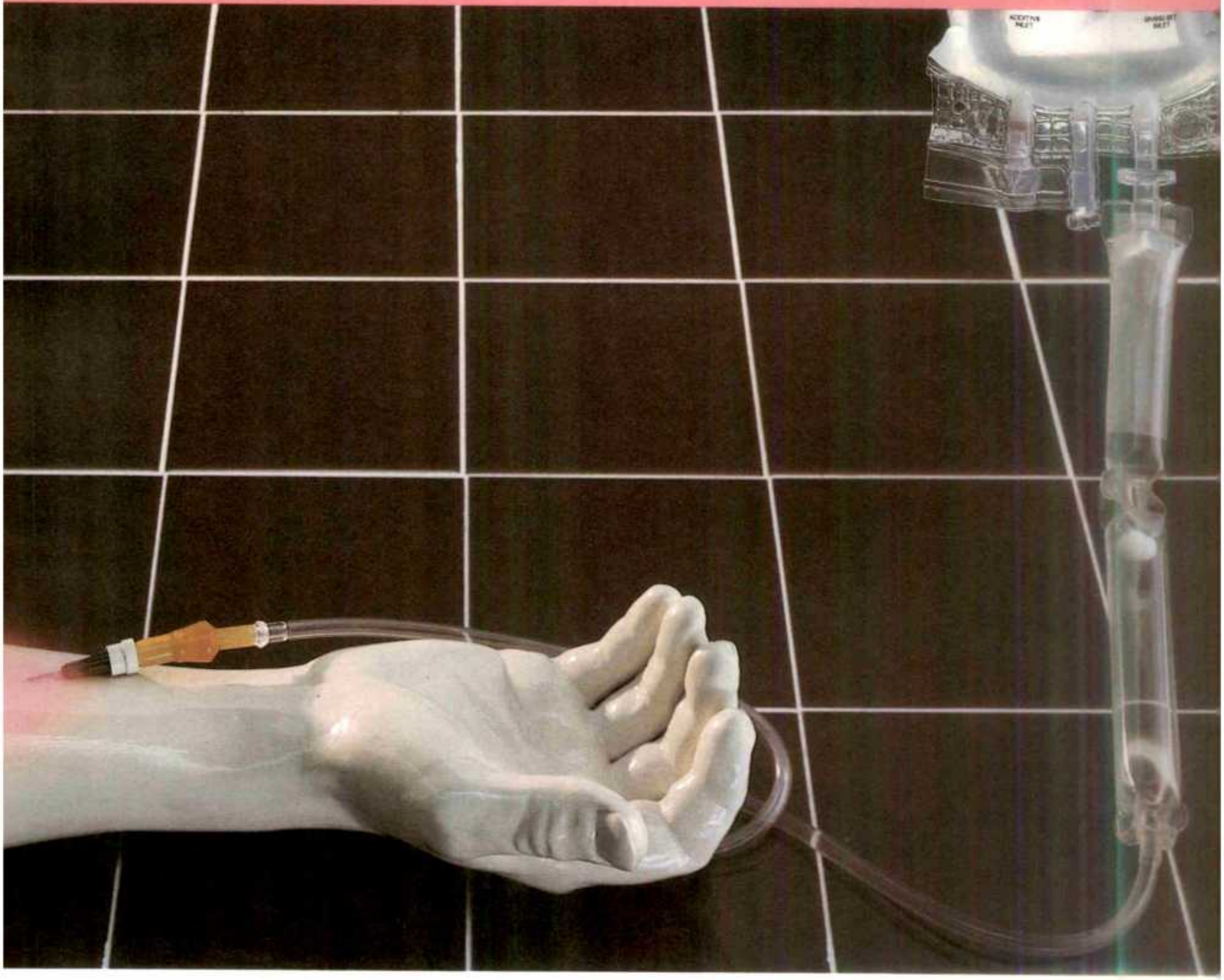

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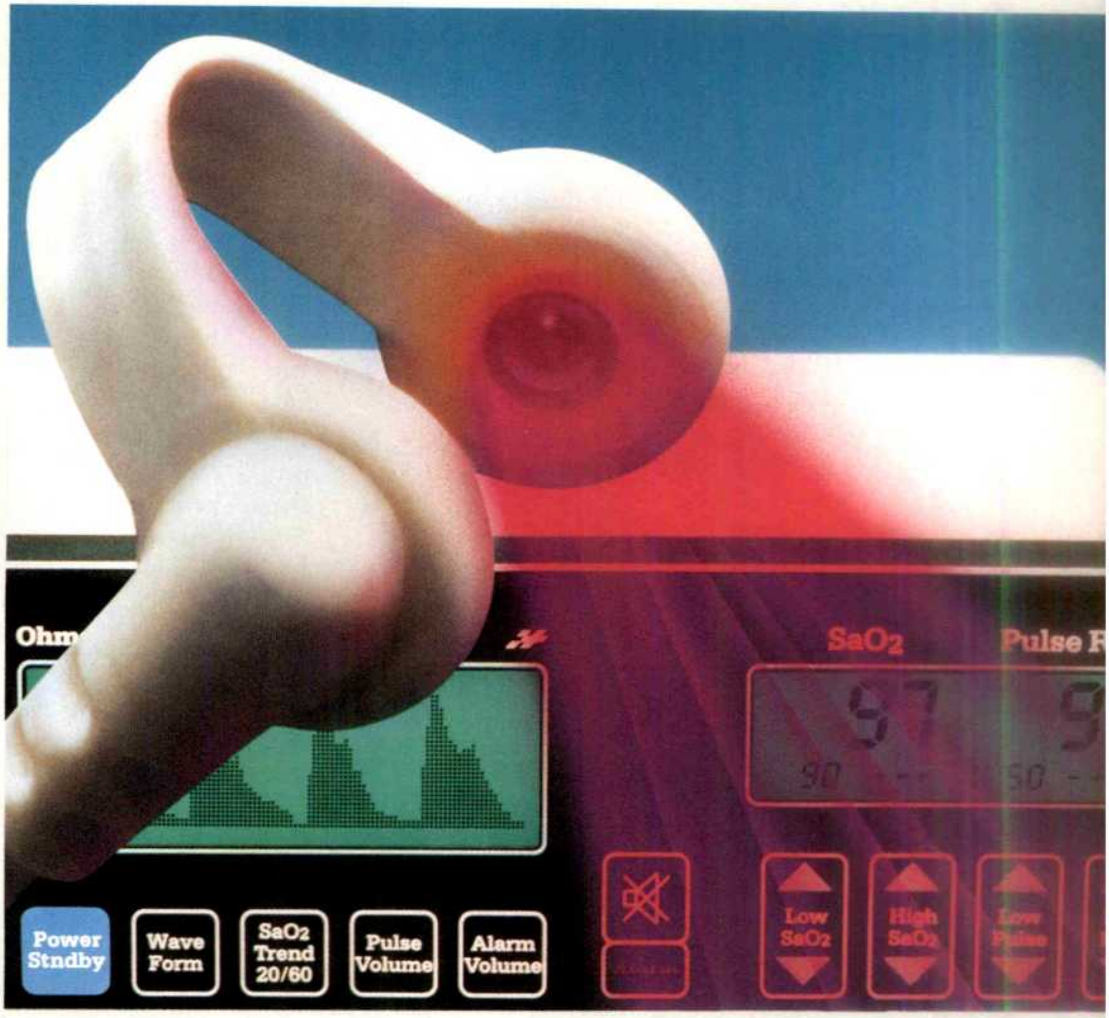

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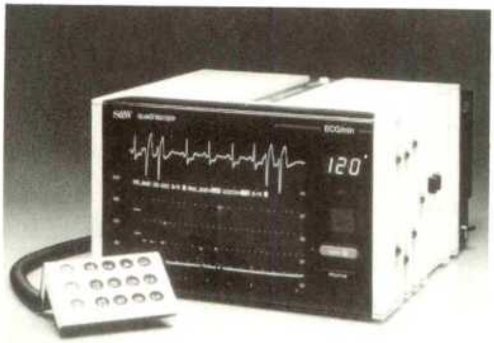

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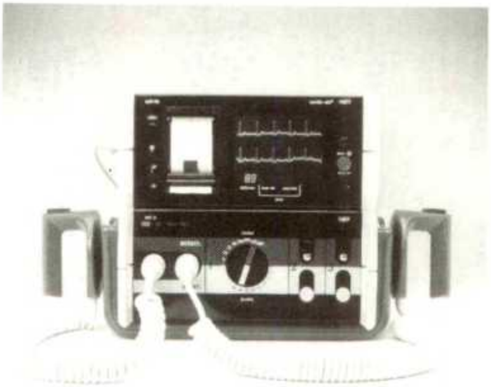

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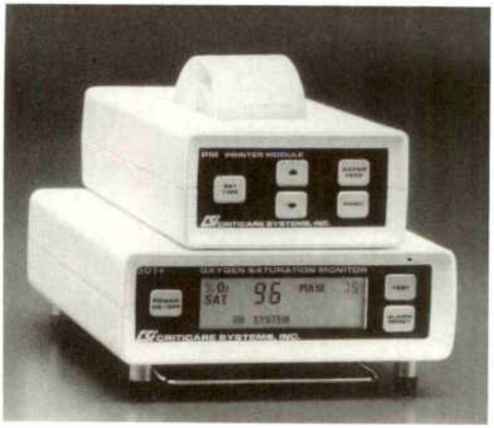

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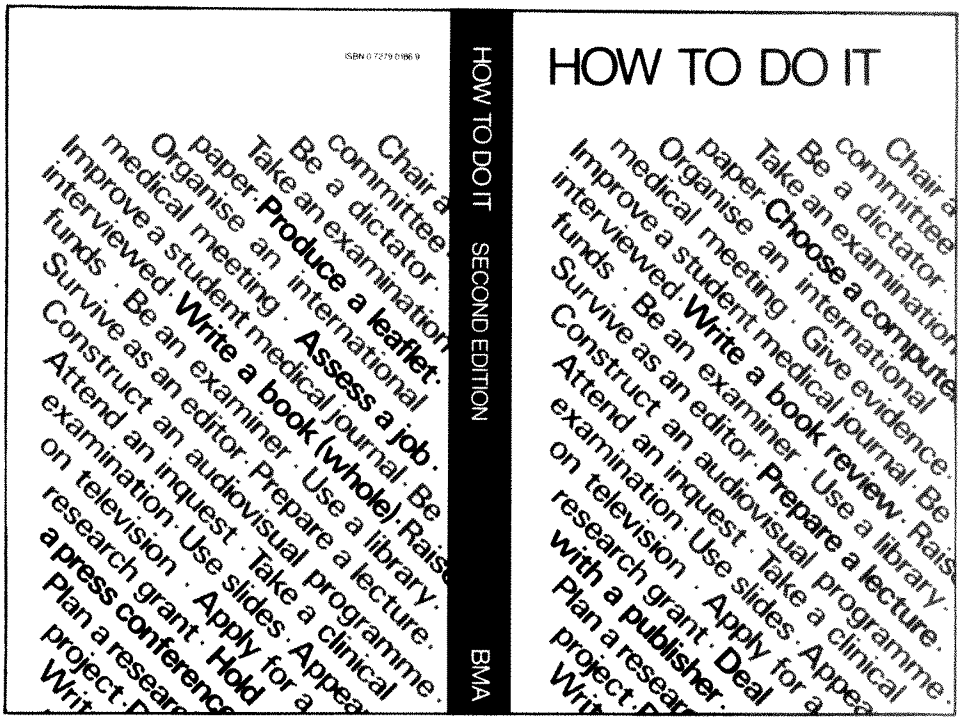
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EDITORIAL

AIDS AND BLOOD TRANSFUSION

From recent media coverage it would be easy to gain the impression that every transfusion carried a significant risk of transmitting AIDS. Public confidence in the Transfusion Service is at risk, and the flurry of enquiries received by many Transfusion Services suggests that at least some patients perceive the risk of AIDS to outweigh by far other worries they may have regarding hospital treatment. A sign of this is the increasing number of requests from patients for autologous transfusion or the collection of blood from relatives (directed donor transfusion) in order to cover an anticipated need during surgery or childbirth. Certainly, both these procedures are, for a proportion of patients, technically possible. Since hospital medical staff and general practitioners may be asked about these possibilities, it is worth considering carefully the arguments for and against these alternative transfusion arrangements. Discussion of currently available information should be sufficient to allow most patients to be reassured regarding what is in fact a negligible risk from blood transfusion.

The Blood Transfusion Service has, for a number of reasons, not endorsed the use of autologous or directed donor transfusions.

People who are in the now well known high risk groups are asked not to donate blood. Published evidence from the U.S.A. (Pindyck et al., 1985), as well as data currently being collected in the U.K., suggest that the vast majority are complying with this request.

More than three million blood donations have been collected in the United Kingdom since October 1985 when laboratory testing for anti-HIV began. Sixty-five positive samples have been identified so far (an incidence of 0.002%) none of which was transfused (DHSS, 1987). To date, 26 cases of HIV infection resulting from blood transfusion have been notified in the U.K.; these are virtually confined to donations collected before laboratory testing was introduced or to blood transfusions received abroad (PHLS Communicable Diseases Surveillance Centre). These include 10 patients with clinical symptoms, only four of whom actually received a transfusion in the United Kingdom. However, it is now well known that a much greater number of recipients of clotting factor concentrates have become infected; in most instances these derive from the use of imported materials collected before the causative agent for AIDS was identified. The occurrence of future cases must still be expected because the incubation period for HIV infections can be as long as several years.

Current tests for HIV antibody do appear to be highly reliable for screening blood donations (Reesink et al., 1986), although it has to be accepted that recently infected people may not have had time to become antibody positive. Typically, seroconversion appears to occur by about 6 weeks (Melbye, 1986), but can take as long as 9 months (Allain et al., 1986). AIDS, or HIV infection outside the high risk groups is still rare in the U.K. and the statistical likelihood of donors giving blood whilst in the early infection phase is very low. Unfortunately, it appears that one instance of this seems to have occurred recently in Scotland, but the widespread publicity given to the case should not be allowed to obscure the fact of its rarity.

Tests for HIV antigen have now reached an advanced state of development (Allain et al., 1986; Lange et al., 1986) and, if necessary, these will be introduced to the routine testing regimen with the aim of detecting newly infected donors. To these may also be added tests capable of detecting HIV variants, in particular the new strain HIV2 that now seems to have reached the United Kingdom.

Autologous donations, either stored frozen or, more usually, collected in the weeks before expected surgery, are sometimes seen as a safe alternative to volunteer donor blood. In the present context of transmitted infections this is theoretically true. However, it must also be borne in mind that there are other risks of transfusion, in particular errors of blood identification and those resulting from incorrect storage or handling of donations. These mishaps are almost certainly more likely to occur during the administrative arrangements that would be necessary for large-scale autologous transfusion. Blood Transfusion Services and hospital blood banks have, over several decades, developed organizational arrangements to minimize chances of fatality through patients receiving either the wrong blood or blood that is infected or mishandled and damaged. The current safety record of transfusion attests to their success.

The value of autologous transfusion is of course negated if a patient's requirement for blood exceeds the amount collected and stored ready for use, in which instances volunteer donor blood must be used also.

Donations from close relatives or even friends of patients are sometimes offered as a way of guaranteeing freedom from transmissable illness. Notwithstanding the chances that such donations may well be incompatible on purely serological grounds, it is now realized that risks from blood from these sources are no less than from random donor blood collected and tested under carefully controlled circumstances. It should also be borne in mind that the consequences of a mishap arising under these arrangements would be particularly unfortunate.

Enthusiasm for autologous transfusion once the arrangements have been established is not always maintained. Attendance at hospital to provide blood donations will be time consuming to the patient as well as for those responsible for its organization. Those working in blood banks recognize how difficult it is to avoid identification errors and clerical errors, even when regular trained staff are involved; how much more difficult will this be when staff less familiar with such procedures must be involved? The blood wastage rate is bound to be high if, as at present, an average of only 40% of the blood crossmatched for patients is actually used. Cancelled surgery, by no means an infrequent occurrence, is likely to cause additional difficulties because it will almost inevitably increase the chances that autologous donations will become wasted. Autologous donations collected under these circumstances are unlikely to be usable within the general pool of random donations—how many patients expecting to enter hospital would be likely to satisfy criteria for donor eligibility, especially with regard to concurrent drug therapy?

Setting up organizational arrangements for collection of blood from patients or their relatives would undoubtedly be costly. Cost is, of course, not of prime concern to patients under these circumstances and in any case must be outweighed by medical and ethical considerations. It should be remembered within the profession, however, that most donations collected by Transfusion Services are subdivided into components, for example plasma, platelets and red cells, each destined for categories of patients with particular requirements for transfusion. In that way any given donation may benefit several patients, with corresponding financial savings, as well as savings in the total number of donations required.

The risks of transfusing volunteer donor blood, low as they are, still cause concern to many members of the profession. What, then, can be constructively offered to improve patient safety? Certainly, the excellent safety record of transfusion over many years may have induced a degree of complacency. Current concern about transmissable infection should force doctors to make a more careful risk–benefit assessment of every proposed transfusion. Economy in the use of red cell transfusions could certainly be promoted more vigorously. Haemodilution techniques, well established in the field of cardiac surgery, could be explored more widely. It should be borne in mind that approximately 75% of transfusion recipients are given 3 units or less. It could be argued that, for a proportion of these patients, red cell transfusions were unnecessary and that haemodilution through use of crystalloids or colloids was in the patient's interest. Indeed, preoperative haemodilution, which may involve removal of blood just before surgery and replacement by synthetic volume expanders has been advocated on sound physiological principles. The procedure also provides some blood for replacement of surgical losses should the haemoglobin decrease to less than 10.0 g dl^{-1}.

In conclusion, it is still possible to state that the safety of blood transfusion in the United Kingdom remains exceptionally high. The advent of AIDS has, of course, vastly increased our awareness of transfusion risks—the actual risks, however, remain small and little changed. There is no evidence that autologous donations, or donations from relatives, are necessary or that they will provide any increased level of protection. Of course this situation must be reviewed continually. The prevalence of HIV infection, in particular that relating to people outside currently recognized high risk groups, must be carefully monitored. These anxieties, both public and within the medical profession, should discourage doctors from giving blood transfusions unless these are clearly necessary for the patient's recovery. Increased discrimination in the use of blood transfusion, together with continued improvements in the already highly effective procedures for laboratory screening of donations, should ensure that the current level of safety in blood transfusion is maintained.

J. A. F. Napier

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ANAESTHESIA FOR CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

A Review of 350 Patients

N. J. MACDONALD, G. J. FITZPATRICK, K. P. MOORE, W. S. WREN AND M. KEENAN

SUMMARY

The anaesthetic management of 350 consecutive patients with congenital hypertrophic pyloric stenosis over an 8-year period is reviewed. The anaesthetic technique is discussed and the complications encountered reviewed. The morbidity rate was 15.9%. The anaesthetic related morbidity rate was 3.7%. One patient in the series died (0.27%) 8 weeks after pyloromyotomy, as a result of an underlying myopathy.

Congenital hypertrophic pyloric stenosis, with an incidence of 3 per 1000 live births (Editorial, 1984), is the second commonest reason for surgical intervention in the first 6 months of life. Ramstedt's pyloromyotomy is the treatment of choice.

Bennet (1968) and Touloukain and Higgins (1983) have described the complex electrolyte and metabolic disturbances which occur in this condition, and which stem from the loss of hydrogen, chloride, sodium, potassium and water in the vomitus. Initially, the kidney compensates by excreting sodium and potassium bicarbonate, but when hypokalaemia and hyponatraemia supervene an acid urine is produced, aggravating the hypochloraemic hypokalaemic alkalosis. A compensatory respiratory acidosis is usually present. Lactic acidosis secondary to hypovolaemic shock occurs in severe cases. These starving infants are prone to hypoglycaemia.

Although the management of this condition has improved considerably, some published series show a small but significant mortality which ranges from 0.32% to 2% (Bell, 1968; Daly and Conn, 1969; Kiely et al., 1981; Gray, Gear and Stevens, 1984). We report the experience of the anaesthetic management of congenital hypertrophic pyloric stenosis in 350 consecutive patients over an 8-year period in one hospital.

PATIENTS AND METHODS

The names of all patients who underwent pyloromyotomy between January 1, 1977 and December 31, 1984 were taken from the operating theatre record books. All of the case notes were located and included in the study.

Fourteen patients (4%) had been admitted to hospital for other reasons when the symptoms of pyloric stenosis developed. The diseases present in this group of patients are listed in table I. For the purposes of the study they were designated group A. The statistics for the variables "time from admission to surgery" and "days spent in hospital after operation" were calculated both for all patients (350) and with group A excluded (336).

Management

After admission to hospital the infants were resuscitated with appropriate i.v. fluids and electrolyte solutions. A nasogastric tube (size 8 French gauge) was passed and the stomach kept empty by frequent aspiration. Estimations of blood glucose concentration were made 2–4 hourly using reagent strips (Ames Dextrostix).

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TABLE I. *Conditions present in patients who were in hospital when the symptoms of pyloric stenosis first occurred*

Condition	No. patients
Congenital cardiac anomaly	8
Tracheo-oesophageal fistula	2
Cystic fibrosis	1
Congenital myopathy	1
Seborrhoeic dermatitis	1
Viral meningitis	1
Total	14

Initial i.v. therapy was always with an electrolyte/dextrose solution, usually 2.5% dextrose in saline 0.45 g at 150 ml kg^{-1} day^{-1}. Additional i.v. fluid with physiological saline (sodium chloride 0.9 g%) was given to replace nasogastric losses. Potassium chloride 2 mmol dl^{-1} was added to the i.v. fluids once urine flow had been established. Occasionally, an infusion of plasma (10–15 ml kg^{-1}) was required for patients presenting in hypovolaemic shock.

Frequent assessments, both clinical and biochemical, were mandatory and resuscitative efforts adjusted accordingly. The infant was deemed fit for surgery when fluid and electrolyte balance was restored to normal. Premedication was with atropine 0.02 mg kg^{-1} i.m., but was omitted if body temperature exceeded 37.5 °C.

The patient was transferred to the operating theatre in a neutral thermal environment. Heat loss was minimized during surgery by keeping the environmental air temperature at 23–25 °C, and by using a thermostatically-controlled heated water mattress.

Before the induction of anaesthesia the nasogastric tube was aspirated (and left in place). Anaesthesia was induced either by inhalation or with a rapid sequence i.v. technique using a "sleep dose" of thiopentone. Suxamethonium 1–2 mg kg^{-1} was administered, the trachea intubated and anaesthesia maintained with 66% nitrous oxide in oxygen supplemented with a volatile anaesthetic agent. Muscular paralysis was usually achieved with a competitive neuromuscular blocking agent or with intermittent injections of suxamethonium. Ventilation was controlled mechanically using a suitable ventilator, or manually via the Jackson–Rees modification of Ayres' T-piece (both techniques are used in this teaching hospital). Arterial pressure, the electrocardiogram and rectal temperature were monitored routinely. A precordial stethescope was used frequently.

At the end of surgery neuromuscular blockade was reversed and the trachea extubated when the infant was fully awake and moving all four limbs vigorously. The patient remained under close observation in the recovery unit for at least 1 h, and during this period blood glucose concentration was estimated using a "Dextrostix". The patient returned to an infant ward staffed by nurses experienced in the postoperative care of infants.

I.v. fluids were continued with 2.5% Dextrose in saline 0.45 mg% at 4 ml kg^{-1} h^{-1} until oral feeding was re-established.

The current practice is to leave the nasogastric tube *in situ* for 12 h. If, at 24 h, there is no vomiting, a trial feed of dextrose 100 ml, electrolyte and water is given. If this is tolerated then feeds are recommenced, starting with one-quarter strength and gradually building up to full strength (Leahy and Fitzgerald, 1982).

RESULTS

Of the 350 patients in the series, 294 (84%) were male and 56 (16%) were female. The mean values, standard deviations and ranges for age (weeks) and weight (kg) are given in table II. Three hundred and fifteen (90%) patients were full term (38–42 weeks gestation) at birth and 11 (3.1%) were born at less than 35 weeks gestation.

Pyloric stenosis developed in eight patients who were admitted to hospital because of congenital heart disease (table I). (This hospital is the

TABLE II. *Mean, SD and range for age, weight, time from admission to surgery, duration of anaesthesia, time on i.v. fluids after operation and days spent in hospital after operation*

Variable	Mean	SD	Range
Age (weeks)	6.2	3.4	1–30
Weight (kg)	3.76	0.76	1.8–8.4
Time from admission to surgery (h)			
All patients	51.3	55.9	2–200
Group A excluded	46	36.2	2–336
Duration of anaesthesia (51% of patients) (min)	44.3	13.6	15–100
Time on i.v. fluids post-op. (h)	48.2	25.5	6–240
Time in hospital post-op. (days)			
All patients	6.4	6.4	2–66
Group A excluded	5.9	4.8	2–43

National Centre for paediatric heart disease, with 500–600 referrals per year.)

The mean interval between admission and surgery was 51.3 h (table II). One hundred and forty-five (41.4%) infants were not dehydrated on admission. However, of these, 86 (59.3%) had been actively treated in other hospitals before their transfer (table III). One hundred and ninety-three (55.1%) patients had chloride concentrations below normal (table III). Seventy-one (20.3%) had serum potassium values below normal (table III). Atropine was given i.m. in 287 (82%) infants as a premedicant, and omitted in 63 (18%), 26 of whom had a rectal temperature of 37–38 °C. The other 37 were brought to theatre unpremedicated and received atropine i.v. at induction.

Anaesthesia was induced i.v. in 210 (60%) patients and by inhalation in 140 (40%). The relative proportions of i.v. and inhalation inductions in each year are displayed in figure 1. In 1977, anaesthesia was induced i.v. in six (14.6%) patients; in 1984, 35 (85.4%) received an i.v. induction. One hundred and ninety-nine (57%) patients were ventilated automatically and 151 (43%) were manually ventilated using the Jackson–Rees modification of Ayre's T-piece.

The duration of anaesthesia was recorded in 179 (51%) patients and was not available in 171 (49%). The mean value was 44.3 min (SD 13.4, range 15–100). The mean time for which i.v. fluids were required after operation was 48.2 h (SD 25.5, range 6–240) (table II).

TABLE III. *Degree of dehydration, and serum chloride and potassium concentrations, on admission. (Of those not dehydrated, 59.5% had been actively treated in another hospital before transfer here)*

	No. patients
Degree of dehydration	
None	145 (41.4%)
Mild	154 (44%)
Moderate	40 (11.4%)
Severe	11 (3.2%)
Serum chloride (mmol litre^{-1})	
> 95	157 (44.9%)
90–95	88 (25.1%)
80–90	68 (19.5%)
< 80	32 (10.5%)
Serum potassium (mmol litre^{-1})	
> 3.5	276 (78.7%)
3.0–3.5	42 (12%)
< 3.0	32 (9.3%)

Morbidity and mortality

One patient (0.27%) known to have a rare progressive muscle disorder died 8 weeks after pyloromyotomy. This patient was the only infant in the series to have his operation performed under local infiltration anaesthesia (using 3 ml of 0.25% lignocaine).

The morbidity rate was 15.9%. This was arbitrarily divided into surgical and anaesthetic morbidity. The surgical morbidity rate was 12.2%; this included wound infections, wound dehiscence, persistent vomiting, delayed feeding and urinary tract infections. The anaesthetic

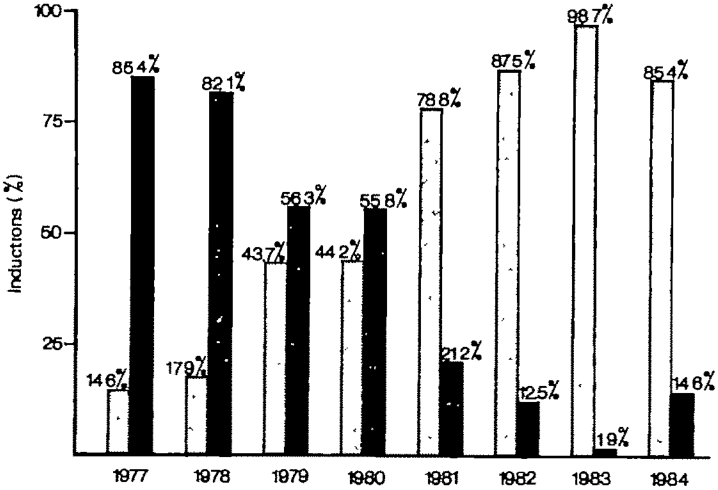

FIG. 1. Percentage of inhalation (black columns) and i.v. inductions in each year from 1977 to 1984.

TABLE IV. *Causes of morbidity related to anaesthesia*

Cause	No. patients	Comment
Upper respiratory tract infection	3	Consisted of mild pyrexia, nasal snuffles, and/or pharyngitis. There was no clinical or radiological evidence of lower respiratory tract infection.
Lower respiratory tract infection	5	Two patients had a preoperative upper respiratory tract infection. One patient had had respiratory distress syndrome requiring controlled ventilation as a neonate. One patient had congenital heart disease and cardiac failure before operation.
Delayed recovery from anaesthesia	3	See text
Postoperative cyanotic attack	1	See text
Postoperative stridor	1	Persisted for 6 h after operation. Treated with humidified oxygen.

related morbidity rate was 3.7%. This included all patients in whom morbidity was definitely or possibly related to anaesthesia. These are listed in table IV. All of these patients made a full recovery.

DISCUSSION

No patient died as a result of congenital hypertrophic pyloric stenosis or pyloromyotomy in this hospital during an 8-year period in which 350 pyloromyotomies were performed.

This compares favourably with several reports in which a small but definite mortality was recorded (Bell, 1968; Kiely et al., 1981; Gray, Gear and Stevens, 1984). One patient, suffering from myotubular myopathy and requiring mechanical ventilation from birth, died 8 weeks after pyloromyotomy. The operation was performed under local infiltration analgesia and both surgery and anaesthesia were uneventful.

The morbidity rate was 15.9%. All patients made a full recovery. Gray, Gear and Stevens (1984) report a complication rate of 20%; Dubousset (1973) had two cases of gram-negative septicaemia from which both patients subsequently died, in a series of 109 patients.

Four infants developed postoperative complications which warrant further discussion.

Patient 1. A 49-day-old full term male infant weighing 3.6 kg presented with pyloric stenosis. He was mildly dehydrated on admission and biochemical analysis revealed a hypochloraemic alkalosis. Twenty-four hours later, following correction of hydration with i.v. fluids, he was deemed fit for surgery. Atropine 0.06 mg i.m. was given as a premedicant. Before induction of anaesthesia the nasogastric tube was aspirated and anaesthesia induced with halothane and nitrous oxide in oxygen. Following the administration of suxamethonium 6.25 mg, the trachea was intubated. The lungs were ventilated manually using the Jackson–Rees modification of Ayre's T-piece, and anaesthesia was maintained with halothane and nitrous oxide in oxygen. Surgery was uneventful and lasted 20 min. The trachea was extubated once the infant was fully awake and moving all limbs. Shortly after extubation of his trachea he was returned to the ward where, 30 min after anaesthesia, he had an apnoeic attack and became cyanosed. He responded to manual ventilation with 100% oxygen via a face mask.

Patient 2. A 17-day-old 4.06-kg male infant presented for Ramstedt's pyloromyotomy. After aspiration of the nasogastric tube, anaesthesia was induced with thiopentone 12.5 mg and tracheal intubation was facilitated with suxamethonium 6.25 mg. Cricoid pressure was maintained from the start of the induction until correct placement of the tracheal tube was confirmed by auscultation. The lungs were ventilated mechanically using a

Servo 900C ventilator. Anaesthesia was maintained with 0.5% halothane and nitrous oxide in oxygen. Pancuronium 0.3 mg was administered. Surgery and anaesthesia were uneventful. The duration of anaesthesia was 45 min. Upon cessation of anaesthesia, and after adequate antagonism of neuromuscular blockade, with neostigmine 0.24 mg and atropine 0.12 mg—as shown by an adequate response to peripheral nerve stimulation—the infant developed a jerky, inadequate ventilatory pattern. Blood-gas analysis was normal. He was transferred to the intensive care unit and required ventilatory assistance. Following 7 h of i.v. fluid therapy and intermittent positive pressure ventilation, he was weaned from IPPV and the trachea was extubated. The patient made an uneventful recovery. Blood sugar concentration was normal throughout the intra- and post-operative periods.

Patient 3. A 42-day-old full-term female who weighed 4.7 kg presented with a 3-day history of vomiting and was mildly dehydrated on admission. She was resuscitated for a 24-h period, before undergoing surgery. Atropine 0.08 mg was given i.m. as a premedicant. A rapid sequence i.v. induction was used in this patient with thiopentone 20 mg and suxamethonium 7.5 mg. After intubation of the trachea, the lungs were ventilated mechanically, anaesthesia was maintained with nitrous oxide in oxygen, and neuromuscular blockade was achieved with pancuronium 0.4 mg. This child was given morphine 0.4 mg during the operation.

After antagonism of neuromuscular blockade with neostigmine 0.28 mg and atropine 0.14 mg, the infant remained drowsy and unresponsive. Spontaneous ventilation was inadequate. Nalorphine 0.5 mg and later naloxone 40 µg failed to produce significant improvement in the level of consciousness, or ventilation.

Blood sugar concentration, serum electrolyte concentrations and the chest x-ray were normal. Blood-gas analysis showed a respiratory acidosis (pH 7.23: $P\text{CO}_2$ 8 kPa; Pa_{O_2} 37 kPa; HCO_3 24.6 mmol litre^{-1}). She was transferred to the intensive care unit for controlled ventilation. Eighteen hours after operation spontaneous breathing was adequate and her trachea was extubated. She remained drowsy for a further 24 h. There were no sequelae.

Patient 4. A 3.7-kg male infant presented for Ramstedt's pyloromyotomy. Again, a rapid sequence induction was used with thiopentone 20 mg and suxamethonium 5 mg. Anaesthesia was maintained with nitrous oxide in oxygen, and pancuronium 0.4 mg was the neuromuscular blocking agent used. The lungs were mechanically ventilated. In this patient fentanyl 12.5 µg was given during the operation. On completion of surgery, residual neuromuscular blockade was antagonized with neostigmine 0.2 mg and atropine 0.1 mg. However, the infant failed to resume spontaneous breathing and required ventilatory assistance for 60 min. Subsequent recovery was uneventful.

Three of the patients in this series were in extremis on admission as a result of severe dehydration. They had marked hypochloraemic alkalosis with serum chloride concentrations ranging from 44 to 67 mmol litre^{-1}, and a serum potassium concentration of less than 2.5 mmol litre^{-1}. Admission to the intensive care unit and meticulous correction of metabolic derangement, which took 3–7 days, resulted in uneventful surgery and anaesthesia. Two of these three patients were discharged home within 12 days of surgery. The third developed a septicaemia on the 10th day after operation, but was eventually discharged home well after 5 weeks. It is essential that any underlying metabolic derangement and dehydration are completely corrected before surgery is contemplated. As pointed out by Steven and Allen (1973), Ramstedt's pyloromyotomy is an elective operation. Emergency surgery for this condition is never necessary, nor is it desirable.

Anaesthetic technique

In 1973, Steven and Allen recommended inhalation induction as the method of choice for pyloromyotomy. The widespread use of Sellick's manoeuvre (Sellick, 1961) associated with a rapid sequence i.v. induction in adults, has spread to paediatric anaesthesia and has been recommended as the technique of choice by Dierdorf and Krishna (1981), and Battersby and his colleagues (1984). As can be seen from figure 1, anaesthesia is induced in the vast majority of patients in this unit by this method. In our series both techniques proved safe and no case of aspiration occurred. The safety of induction depends upon ensuring, as far as possible, that the stomach is emptied, by prior aspiration of the nasogastric tube.

The nasogastric tube was left in place. It facilitated the surgeon's testing the integrity of the bowel wall after pyloromyotomy. A small volume of air was injected down the nasogastric tube and the surgeon manipulated it into the duodenum and occluded the bowel lumen a short distance proximal and distal to the incision. Mucosal perforation would have been indicated by leakage of air.

Anaesthesia was maintained with 60% nitrous oxide in oxygen, and supplemented in 171 patients (48%) with a low concentration of a volatile agent. Halothane was used in the majority of patients although, more recently, we have used enflurane or isoflurane. Neuromuscular blockade was maintained in the majority of patients with pancuronium, although in 1984 we used atracurium satisfactorily in nine patients.

The use of opioids in infants is a controversial issue. In our series 11 patients received an opioid during the surgical procedure. Of the five patients who received morphine, three weighed less than 5 kg, and delayed recovery occurred in one of these. The six patients who received fentanyl all weighed less than 5 kg and one case of delayed recovery occurred in this group. Opioid drugs should be used with caution.

It is important to emphasize the need for close observation in the postoperative period. Potentially fatal complications can occur during this time. Hypoglycaemia is always a potential hazard (Pagliara et al., 1973) and was the cause of fatality in Kiely's series (Kiely et al., 1981).

The postoperative feeding regimen, advocated by Leahy and Fitzgerald in 1982, has resulted in a smoother postoperative course with less vomiting. Previously, feeding was attempted 4 h after operation, but this was frequently associated with vomiting.

The morbidity was evenly distributed over the first 7 years. However, there was no morbidity recorded in 1984. There was no significant change in surgical or anaesthetic management in 1984 and we attributed this morbidity rate to randomization. Both surgical and anaesthetic morbidity have occurred since completion of the study in 1985.

In summary, we report on 350 consecutive pyloromyotomies in which there were no deaths either directly or indirectly attributable to the procedure. There was, however, a small but significant morbidity.

The importance of thorough preoperative preparation, careful anaesthesia and close supervision in the postoperative period is stressed.

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EFFECTS OF FASTING AND ORAL PREMEDICATION ON THE pH AND VOLUME OF GASTRIC ASPIRATE IN CHILDREN

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SUMMARY

The pH and volume of gastric aspirate were measured immediately after the induction of anaesthesia in 224 healthy children to determine the effects of decreasing the period of fasting and of giving oral premedicants before anaesthesia. Fasting for less than 4 h was found to increase the volume of gastric aspirate and the risk of developing pulmonary aspiration syndrome. Trimeprazine syrup was found to increase the pH of the gastric contents, and decrease the likelihood of the pulmonary aspiration syndrome. There was a significant increase in gastric volume in patients premedicated with temazepam elixir which did not occur in patients given temazepam capsules. These results support the custom of fasting patients for at least 4 h before anaesthesia and indicate that oral premedicants and their vehicles can have significant effects on the stomach.

The aspiration of gastric contents remains a major cause of morbidity and mortality related to anaesthesia (Lunn and Mushin, 1982) and, in order to decrease the risk of pulmonary aspiration, it is customary to fast patients for at least 4 h before anaesthesia. However, it was claimed recently that a light meal 2–3 h before surgery did not alter the volume or pH of gastric aspirate in adults at the induction of anaesthesia (Miller, Wishart and Nimmo, 1983). If these results could be confirmed in children, a highly desirable decrease in the duration of fasting would be possible. Although fears that children are at increased risk of developing hypoglycaemia appear to have been unfounded (Redfern, Addison and Meakin, 1986), there is no doubt that they are more likely to become dehydrated or emotionally disturbed as a result of preoperative starvation.

Despite the widespread use of oral sedatives as premedicants in children, there have been no definitive studies of their effects on gastric function. Children in our hospital are routinely premedicated with trimeprazine (Vallergan) before inpatient surgery (Cope and Glover, 1959), although temazepam (Euhypnos) has been introduced recently as a premedicant for outpatients (Greenwood and Bradshaw, 1983). In the present study, the pH and volume of gastric aspirate were measured after the induction of anaesthesia in children to determine the effects of these premedicants, and of fasting for less than 4 h.

PATIENTS AND METHODS

The design of the study was approved by the hospital Ethics Committee and parental consent was obtained. Two hundred and twenty-four healthy children undergoing elective surgery in the afternoon were studied. Approximately half were scheduled for tonsillectomy, whilst the remainder were to undergo minor surgical procedures on the body wall. For most the last main meal consisted of a breakfast of cereals and milk given before 8.00 a.m., after which all oral intake was recorded.

Patients were divided into five groups (table I). Children in group 1, the control group, fasted for a minimum of 4 h and received no premedication. Patients in group 2 received no premedication,

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TABLE I. *Details of patient groups (mean values and range). Statistical differences from controls:* *$P < 0.05$; ***$P < 0.001$

Group	n	Fasting period (h)	Age (yr)	Weight (kg)
1. Control	55	7.1 (4.1–16.7)	6.6 (1–14)	26.1 (10–77)
2A. Drink	34	3.0 (2.1– 3.8)***	8.1 (2–16)	28.1 (13–55)
2B. Drink and biscuits	32	3.1 (2.1– 3.9)***	6.0 (1–12)	22.3 (10–41)
3. Trimeprazine syrup	48	7.2 (4.0–18.2)	5.7 (1–15)	23.8 (12–62)
4. Temazepam elixir	39	7.1 (4.1–17.1)	6.6 (2–16)	25.6 (12–66)
5. Temazepam capsules	16	8.8 (4.2–17.8)	9.1 (4–14)*	32.3 (18–59)*

but were divided into subgroups A and B to receive either a drink of orange squash (10 ml kg^{-1}, maximum 200 ml), or a drink and two plain biscuits, 2–4 h before anaesthesia. Patients in groups 3, 4 and 5 fasted for a minimum of 4 h and received oral premedication. Group 3 received trimeprazine syrup 3 mg kg^{-1} (max. 90 mg) 2 h, group 4 received temazepam elixir 1 mg kg^{-1} (max. 20 mg) 1 h, and group 5 received a similar dose of temazepam in capsule form 1 h, before operation.

Before the induction of anaesthesia, patients were asked to breathe 100% oxygen via an anaesthetic face mask for a few minutes. Anaesthesia was induced with thiopentone 6–8 mg kg^{-1}. This was followed by atropine 0.02 mg kg^{-1}, and suxamethonium 1–2 mg kg^{-1} to facilitate tracheal intubation. Firm sustained pressure was applied to the cricoid cartilage after the loss of consciousness until the tracheal tube was *in situ*. Once the tracheal tube had been fixed in position with adhesive strapping, a 12–14 gauge Ryles tube was passed through the mouth into the stomach. The position of the tube was verified by auscultation over the epigastrium during the insufflation of air, and the gastric contents were aspirated using a 20-ml syringe. Manual pressure was applied over the epigastrium during aspiration—which was repeated in the right and left lateral positions, and in the head down position, for maximal recovery of gastric contents. The Ryles tube was removed. The gastric aspirate was examined for the presence of particulate matter, and its volume was measured using a graduated cylinder. A sample was sent to the laboratory for determination of pH using a Radiometer electrode.

Patients whose gastric aspirate had a pH less that 2.5 and a volume greater than 0.4 ml kg^{-1} were considered at risk of developing the pulmonary aspiration syndrome (Teabeaut, 1952; Roberts and Shirley, 1974). Statistical differences were determined using the Mann–Whitney U test or the χ^2 test where appropriate. The null hypothesis was rejected when $P < 0.05$.

RESULTS

The ages and weights of the patients in the control group and the major test groups were similar (table I). The ages and weights of those children who received temazepam capsules differed significantly from those in the control group, because of the inability of small children to swallow large gelatin capsules.

Unpremedicated patients

Data from the unpremedicated groups are summarized in table II. It will be seen that gastric

TABLE II. *Data from unpremedicated children. Significant differences from controls:* *$P < 0.05$, **$P < 0.01$

Group	Volume of aspirate (ml kg^{-1}) Mean (SEM)	"Dry" patients No. (%)	pH of aspirate Median (Range)	Aspirates with pH < 2.5 and vol. > 0.4 ml kg^{-1} No. (%)
1. Control	0.25 (0.04)	16 (29)	1.9 (1.1–2.5)	12 (22)
2A. Drink	0.39 (0.06)*	4 (12) }*	1.7 (1.3–6.0)	15 (44)*
2B. Drink and biscuits	0.46 (0.06)**	3 (9) }	1.8 (1.4–5.5)	15 (47)*

TABLE III. *Data from controls and children given premedication by mouth. Significant differences from controls:* $*P < 0.05$; $**P < 0.01$; $***P < 0.001$

Group	Volume of aspirate (ml kg^{-1}) Mean (SEM)	"Dry" patients No. (%)	pH of aspirate Median (Range)	Aspirates with pH < 2.5 and vol. > 0.4 ml kg^{-1} No. (%)
1. Control	0.25 (0.04)	16 (29)	1.9 (1.1–2.5)	12 (22)
3. Trimeprazine syrup	0.19 (0.04)	17 (35)	2.2 (1.8–7.8)***	3 (6)*
4. Temazepam elixir	1.10 (0.11)***	1 (3)**	2.2 (1.6–6.5)***	21 (54)**
5. Temazepam capsules	0.32 (0.07)	3 (19)	1.8 (1.5–2.8)	6 (38)

aspirate was significantly increased in children given a drink ($P < 0.05$) or a drink and biscuits ($P < 0.01$) within 4 h of operation. Although the increase in volume tended to be greater in patients given biscuits compared with those given a drink alone, this difference was not significant.

In each group there were a number of patients from whom no aspirate could be obtained. The frequency of these "dry" patients tended to be greater in the control group than in patients fasted for less than 4 h, and when data from the latter groups were combined this difference was shown to be significant ($P < 0.05$). No significant differences were found between the pH values of the gastric content in the unpremedicated groups. pH was less than 2.5 in 93% of the patients from whom an aspirate was obtained.

In both groups fasted for less than 4 h, there was a statistically significant increase in the number of aspirates with a pH of less than 2.5 and volume greater than 0.4 ml kg^{-1}. They were considered at risk of developing pulmonary aspiration syndrome ($P < 0.05$).

Premedicated patients

Table III compares data from the premedicated groups and the unpremedicated controls. Premedication with trimeprazine syrup tended to decrease the volume of aspirate and increase the number of "dry" patients, although this difference was not significant. In contrast, there was a large and statistically significant increase in the volume of aspirate ($P < 0.001$) and fewer dry patients ($P < 0.01$) after premedication with temazepam elixir—a feature not noted in the patients given temazepam capsules. pH was significantly increased in patients premedicated with trimeprazine syrup ($P < 0.001$) and temazepam elixir ($P < 0.001$), but not in patients given temazepam capsules.

Applying the criteria of pH and volume, the risk of developing pulmonary aspiration syndrome was significantly reduced by premedication with trimeprazine syrup ($P < 0.05$), increased by premedication with temazepam elixir ($P < 0.01$) and unchanged by premedication with temazepam capsules.

DISCUSSION

Measurements of the pH and volume of gastric aspirate have been used to identify patients at risk of developing pulmonary damage in the event of pulmonary aspiration. The criteria used, namely, a pH less than 2.5 and a volume greater than 0.4 ml kg^{-1}, were derived from experiments on rabbits and rhesus monkeys which clearly cannot be reproduced in humans. Although there must be some doubt as to whether these criteria can be strictly applied to our patients, they have been used extensively in previous studies in children (see below), and there appears to be general agreement that the effect of aspirated volume is pH dependent (Morgan, 1984).

Our finding that the volume aspirated was greater in children fasted for less than 4 h would seem to be in agreement with the notion of a 2–4 h gastric emptying time (Bannister and Sattilaro, 1962; Green, 1978). The normal variation in gastric emptying time is largely attributable to differences in the physical and chemical properties of the food ingested (Heading, 1980). Thus liquids pass more rapidly from the stomach than solids, and a meal rich in carbohydrates will be evacuated more rapidly than one rich in proteins or fats. The rate of gastric emptying is also affected by the pH and osmolality of the meal. Although there was a tendency for higher volumes in patients given a drink and biscuits compared with those given a drink alone, the difference between the two fed groups was less than might have been anticipated. One reason for this may have been the decision to give orange squash to our patients rather than water. Dilute orange squash, which has a pH of approximately 3.2 and an osmolality of 269 mmol kg,$^{-1}$, could have delayed gastric emptying in both groups. Whilst the choice of the test drink was largely dictated by custom, it was thought that many children would refuse to drink water.

The results of the present study apparently conflict with the findings of Miller, Wishart and Nimmo (1983). These authors found no difference in the volume of the gastric aspirate at induction of anaesthesia in 22 adult patients fasted overnight, compared with 23 patients fed on the morning of surgery. They concluded that a fast of 2–3 h was adequate to ensure the minimum gastric volume after a light breakfast. Although gastric stasis is said to be common in neonates (Kliegman and Fanaroff, 1983) we have been unable to find any evidence that the rate of gastric emptying in older children differs from that in adults. A more likely explanation for the discrepancy is that many of the fed patients in the adult study were fasted for longer than anticipated. Despite the fact that breakfast was permitted 2–3 h before surgery, 10 patients fasted for longer than 4 h, and the mean fasting time for the group as a whole was 3.8 h.

Our results confirm those of earlier studies which showed that the pH of gastric contents is less than 2.5 in the great majority of anaesthetized children (Salem et al., 1976; Goudsouzian et al., 1981; Yildiz et al., 1984; Manchikanti et al., 1985). The volumes of aspirate obtained from our control group (tables II and III) were somewhat less than those obtained in previous studies. This may be the result of methodological differences such as the use of premedicants in most of the previous studies, and the use in some of Salem sump tubes to aspirate the stomach. Whilst no method using a gastric tube can guarantee to empty the stomach completely, it may be that vented sump tubes are more efficient than the single-lumen Ryles tubes used in our study. However, when comparing the results from groups within the present study, the use of a standard method to obtain samples should minimize the importance of any constant error.

Although all the patients in the control group had fasted for a minimum of 4 h (table I), 17 patients received a drink and 18 patients received a drink and two biscuits 4–6 h before anaesthesia. However, no significant difference in the pH or volume of the aspirate or the number at risk of aspiration was found between these patients and the remaining 20 patients of the control group who had fasted for longer than 6 h.

Trimeprazine is a mild phenothiazine sedative with antihistaminic and anticholinergic properties (Vickers, Schnieden and Wood-Smith, 1984). The latter may account for the increase in pH and the trend towards a decrease in volume in those patients premedicated with trimeprazine syrup (table III). Indeed, similar results have been obtained in children premedicated with atropine and glycopyrrolate (Salem et al., 1976). Temazepam, on the other hand, is a short acting benzodiazepine which should be devoid of any direct gastrointestinal actions (Gilman, Goodman and Gilman, 1980). For this reason we supposed that the observed increase in the volume of the stomach contents after temazepam elixir might have been caused by one or more constituents of the vehicle. This hypothesis would appear to be supported by our results with temazepam capsules (table III).

Water insoluble temazepam is prepared as an elixir with approximately 9% ethanol, 45% sorbitol and 50% glycerol, all of which can produce significant gastrointestinal effects. Ethanol is a very effective stimulant of gastric acid secretion, possibly acting directly on the gastric mucosa, but also by releasing gastrin from cells in the antral region of the stomach (Gilman, Goodman and Gilman, 1980). Sorbitol and glycerol are osmotically active in the concentrations given (Reynolds, 1982), and there is evidence that glycerol produces gastric irritation (Staples, Misher and Wardell, 1967). The increase in pH seen in patients given temazepam elixir, but not in those given temazepam capsules, is attributed to the dilution of gastric acid by mucus secretion and fluid drawn into the stomach by osmosis.

Under the conditions of the present study there was an increase in the volume of aspirate and the number of patients at risk of developing pulmonary aspiration syndrome when small amounts of food or drink were given within 4 h of operation. Thus the practice of fasting patients for at least 4 h before anaesthesia would appear to be justified. However, aspiration of gastric contents may also cause injury, even death, if the airway is blocked by large particles of food. In the present study identifiable food residue was found in the gastric aspirates of three patients given biscuits within 4–6 h, and in 13 patients given biscuits within 4 h, of operation. No solid particles were found in the aspirates of patients denied food for longer than 6 h, supporting the view that large meals should be prohibited within 6 h of operation.

The study also demonstrated that oral premedicants and their vehicles may have significant effects on the stomach. Trimeprazine syrup, an oral premedicant used commonly, was found to increase pH and decrease the risk of developing pulmonary aspiration syndrome. Temazepam in the form of a low-alcohol elixir, but not as capsules, was found to increase the volume of aspirate and the risk of lung damage in the event of pulmonary aspiration.

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PRICK TESTS IN THE DIAGNOSIS OF ANAPHYLAXIS TO GENERAL ANAESTHETICS

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SUMMARY

Pre-charged prick tests and intradermal skin tests (two dilutions) were tested simultaneously in 79 patients using seven drugs (suxamethonium, gallamine, alcuronium, pancuronium, vecuronium, fentanyl and thiopentone) commonly administered during general anaesthesia. Fifty-seven of the patients had suffered anaphylaxis to anaesthetics: 50 had been tested previously (19.5 ± 13.5 months) by intradermal tests (group 1) and seven were tested for the first time (group 2). Six patients had suffered a side effect during anaesthesia which was unrelated to anaesthetic agents (group 3) and 16 were control subjects (group 4). Prick and intradermal skin tests were simultaneously positive in 98 instances out of 553 (17.7%) and negative in 440 out of 553 (79.6%)—a correlation of 538 out of 553 (97.3%; $P < 0.001$). In groups 1, 2 and 3 the correlation was 426 out of 441 (96.6%; $P < 0.001$). In group 1, a correlation was observed between the diameters of the weals ($r = 0.5$; $P < 0.001$) obtained by prick and intradermal skin tests, and between the diameters of the flares ($r = 0.5$; $P < 0.001$).

Anaphylaxis to agents used during general anaesthesia is common. About 1 patient in 1500 to 1 in 5000 of those anaesthetized is affected (Clarke et al., 1975; Laxenaire et al., 1982; Hatton et al., 1983; Youngman, Taylor and Wilson, 1983; Beard and Jick, 1985; Watkins, Wild and Clarke, 1985; Vervloet, 1985) with an estimated mortality of 1 in 40000 (Laxenaire et al., 1982; Hatton et al., 1983; Vervloet, 1985). Anaphylaxis occurs most often in women (70% of reported cases) (Clarke et al., 1975; Leynadier, Luce and Dry, 1984), but cannot be predicted readily (Watkins, Wild and Clarke, 1985). Allergy to neuromuscular blocking drugs appears to be the major mechanism, possibly as a result of allergy to the quaternary ammonium groups present in these drugs (Baldo and Fisher, 1983a, b; Harle, Baldo and Fisher, 1984; Vervloet, Arnaud et al., 1985a).

Specific IgE antibodies have been demonstrated (Baldo and Fisher, 1983a, b; Harle, Baldo and Fisher, 1984), and histamine can be released *in vitro* when the assay is potentiated with deuterium water (Vervloet, Arnaud et al., 1985a). Inhibition of histamine release can be obtained with choline, which acts as a monovalent hapten (Vervloet, Benzarti et al., 1985).

The diagnostic value of intradermal skin tests (IST) is accepted generally (Fisher, 1979; Youngman, Taylor and Wilson, 1983; Leynadier, Luce and Dry, 1984; Vervloet, 1985), but they are time-consuming since two (or more) drug concentrations must be tested, and an interval of 20 min allowed between each injection (Leynadier, Luce and Dry, 1984). The technique cannot be used routinely to test patients prospectively before each anaesthetic.

To determine the value of a prick-test using a pre-charged needle (Stallerpoint), IST and prick tests were compared in 57 patients with a history of anaphylaxis to anaesthetic agents, and in 22 control patients.

PATIENTS, MATERIALS AND METHODS

Patients

Group 1. All 50 patients of this group (table I) had experienced an anaphylactic reaction, the signs of which had become evident within 10 min of the injection of the anaesthetic. They had demonstrated a variety of symptoms including tachycardia, cardiovascular collapse, rash and, in

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TABLE I. *Details of patients and control subjects. † Mean ± SD and range*

	Sex	Age (yr)	Diagnosis	Previous skin tests
Group 1 (n = 50)	41F/9M	38.8 ± 11.4 (19–67)†	Anaphylaxis to anaesthetics	Yes: 19.5 ± 13.5 (2–57)† months earlier
Group 2 (n = 7)	6F/1M	32.6 ± 11.8 (20–53)	Anaphylaxis to anaesthetics	No
Group 3 (n = 6)	3F/3M	45.2 ± 18.6 (29–79)	Side effect during anaesthesia	Yes: 22.0 ± 6.4 (11–30) months earlier
Group 4 (n = 16)	10F/6M	30.3 ± 11.3 (22–56)	Control subjects	No

Table II. *Results of skin tests in group 1. Size (mm) of weal (W) or flare (Fl.). — = Test not performed. S = Suxamethonium; G = gallamine; A = alcuronium; P = pancuronium; V = vecuronium; F = fentanyl; T = thiopentone*

Patient (Sex)	Age (yr)	Time between IST (months)	Drugs	Skin tests								Prick tests	
				First IST				Second IST					
				1:1000		1:100		1:1000		1:100			
				W	Fl.	W	Fl.	W	Fl.	W	Fl.	W	Fl.
1 (F)	47	49	S	7	30	—	—	8	24	—	—	0	0
			G	8	20	—	—	0	0	6	12	0	0
			A	5	20	—	—	0	0	0	0	0	0
			F	—	—	—	—	6	25	—	—	0	0
2 (F)	34	25	S	0	0	9	50	5	22	—	—	6	14
			G	0	0	10	25	0	0	0	0	4	9
			A	10	70	—	—	8	38	—	—	6	24
			T	0	0	5	20	0	0	0	0	0	0
3 (F)	31	7	S	0	0	14	20	0	0	0	0	0	0
4 (M)	46	10	T	8	20	—	—	0	6	0	13	0	0
5 (F)	34	21	S	0	0	0	0	0	6	10	40	8	35
			V	—	—	—	—	10	25	—	—	8	18
			F	5	15	—	—	5	10	—	—	10	25
6 (M)	28	12	G	6	25	—	—	5	14	—	—	0	9
			A	0	0	8	10	0	0	0	9	0	0
			T	0	0	6	20	0	0	0	0	0	0
7 (F)	38	36	S	10	25	—	—	6	20	—	—	8	28
			G	0	0	12	22	6	24	—	—	8	22
			V	—	—	—	—	8	34	—	—	0	0
			T	8	20	—	—	5	20	—	—	0	0
8 (M)	37	26	G	5	20	—	—	0	0	6	30	5	20
			P	5	20	—	—	0	10	8	16	11	22
			V	—	—	—	—	10	35	—	—	5	12
9 (F)	54	26	P	12	30	—	—	0	0	0	0	0	0
10 (M)	61	26	A	14	40	—	—	6	12	—	—	8	22
11 (F)	33	25	S	0	0	12	30	0	0	6	42	5	16
			G	10	30	—	—	10	54	—	—	8	48
			P	12	60	—	—	8	56	—	—	7	36
12 (F)	32	20	G	0	0	0	0	8	30	—	—	10	20
			A	0	0	0	0	6	20	—	—	12	28
			P	10	50	—	—	15	38	—	—	10	30
			V	0	0	10	40	10	20	—	—	5	25
			T	0	0	0	0	8	15	—	—	8	18

TABLE II (*cont.*)

Patient (Sex)	Age (yr)	Time between IST (months)	Drugs	Skin tests								Prick tests	
				First IST				Second IST					
				1:1000		1:100		1:1000		1:100			
				W	Fl.	W	Fl.	W	Fl.	W	Fl.	W	Fl.
13 (F)	26	20	S	0	0	5	20	10	25	—	—	5	20
			G	0	0	5	10	0	0	8	12	0	0
			A	16	50	—	—	10	30	—	—	10	25
14 (F)	42	19	S	5	5	5	10	0	0	10	20	8	20
			G	0	0	0	0	0	0	10	25	5	12
			F	5	5	5	20	0	0	0	0	0	0
15 (F)	51	18	S	10	40	—	—	15	28	—	—	12	30
			P	30	50	—	—	28	56	—	—	18	48
			V	—	—	—	—	20	40	—	—	10	32
			T	0	0	—	—	0	0	0	0	8	26
16 (F)	27	16	G	10	20	—	—	0	0	9	25	0	0
17 (F)	44	15	S	0	0	10	30	16	30	—	—	10	20
			G	0	0	10	25	10	28	—	—	8	30
			A	2	15	6	30	12	25	—	—	10	32
			P	30	75	—	—	16	50	—	—	12	42
			V	25	60	—	—	15	58	—	—	8	35
18 (F)	55	10	S	7	20	—	—	5	18	—	—	8	18
			G	8	25	—	—	5	16	—	—	8	23
			P	0	0	6	18	0	0	0	0	0	0
19 (F)	40	10	S	7	30	—	—	0	0	10	24	7	15
			A	0	0	5	18	0	0	6	20	0	10
20 (F)	45	10	A	8	40	—	—	0	40	5	38	9	30
			P	0	0	10	50	5	30	—	—	5	20
			V	10	50	—	—	10	28	—	—	6	20
21 (F)	28	10	S	9	30	—	—	18	38	—	—	8	32
			G	10	40	—	—	15	45	—	—	8	20
			A	0	0	10	30	10	30	—	—	12	40
			P	7	10	—	—	10	32	—	—	0	0
			V	10	30	—	—	0	0	10	30	8	18
22 (F)	26	9	S	10	40	—	—	12	50	—	—	15	35
			G	12	50	—	—	15	55	—	—	12	40
			A	0	0	6	10	0	0	8	25	9	30
23 (F)	26	8	S	7	22	—	—	6	28	—	—	6	24
			G	10	20	—	—	9	38	—	—	9	34
			A	6	22	—	—	5	18	—	—	7	18
			V	0	0	0	0	8	38	—	—	6	18
			T	0	0	0	0	10	44	—	—	6	26
24 (M)	19	7	S	0	0	10	20	10	28	—	—	8	18
			G	10	25	—	—	12	36	—	—	8	24
			P	11	35	—	—	0	0	0	0	0	0
25 (F)	39	6	S	15	20	—	—	16	34	—	—	7	18
26 (M)	35	7	P	10	12	—	—	10	30	—	—	10	26
			V	0	0	14	35	20	38	—	—	8	18
27 (F)	44	6	G	7	30	—	—	8	25	—	—	8	28
28 (F)	45	34	S	10	30	—	—	0	0	9	24	8	12
			P	0	0	8	30	0	0	0	0	0	0
29 (F)	67	10	P	5	15	7	35	12	42	—	—	10	28
30 (F)	31	32	G	5	15	13	30	12	28	—	—	8	36
			V	—	—	—	—	8	20	—	—	0	0
			T	5	20	—	—	0	0	0	0	0	0
31 (F)	42	33	P	5	60	—	—	0	0	0	0	0	0
			T	5	50	—	—	0	0	0	0	0	0

TABLE II (*cont.*)

				Skin tests									
				First IST				Second IST				Prick tests	
				1:1000		1:100		1:1000		1:100			
Patient (Sex)	Age (yr)	Time between IST (months)	Drugs	W	Fl.	W	Fl.	W	Fl.	W	Fl.	W	Fl.
32 (F)	55	8	P	5	20	—	—	0	0	0	0	0	0
33 (F)	42	6	A	8	30	—	—	0	0	0	0	0	0
			V	5	35	—	—	0	0	0	0	0	0
34 (M)	28	7	G	10	12	12	45	0	0	9	62	10	38
			V	0	0	5	10	0	0	0	0	0	0
35 (F)	34	31	F	5	20	5	25	0	0	0	0	0	0
36 (F)	35	30	G	8	10	10	25	0	0	0	0	0	0
37 (F)	29	5	S	0	15	15	40	8	28	—	—	10	20
			G	7	20	—	—	13	38	—	—	6	20
			F	0	0	7	14	0	0	0	0	0	0
38 (F)	27	2	S	0	0	10	45	0	8	10	22	8	24
			G	10	50	—	—	12	56	—	—	8	44
			V	6	20	—	—	11	26	—	—	5	12
39 (F)	45	37	S	10	35	—	—	13	52	—	—	8	21
			G	—	—	—	—	11	33	—	—	7	15
			A	—	—	—	—	11	36	—	—	7	11
			P	—	—	—	—	8	31	—	—	7	21
			V	—	—	—	—	16	52	—	—	8	32
			T	0	0	12	35	0	0	0	0	5	21
40 (F)	59	2	G	0	0	5	10	6	28	—	—	5	10
			P	0	0	10	25	0	0	0	0	0	0
			T	0	0	10	35	0	0	0	0	0	0
41 (F)	54	5	S	0	0	15	60	12	18	—	—	8	28
			G	10	50	—	—	10	22	—	—	8	18
42 (F)	31	2	S	0	0	8	25	11	23	—	—	8	26
			G	5	15	9	15	11	18	—	—	8	32
			V	0	0	11	30	0	0	0	0	0	0
			F	0	0	7	25	0	0	0	0	0	0
43 (F)	35	36	S	5	25	—	—	11	31	—	—	8	12
			A	5	35	—	—	12	42	—	—	6	14
44 (F)	44	36	G	0	0	5	20	0	0	0	0	0	0
			A	0	0	10	40	11	15	—	—	8	18
45 (F)	26	37	A	6	35	—	—	12	88	—	—	7	56
46 (F)	61	57	S	—	—	12	40	12	14	—	—	10	28
47 (F)	26	30	G	10	35	—	—	0	0	10	18	10	18
			A	0	0	5	25	0	0	0	0	0	0
48 (M)	38	36	S	5	10	5	10	0	0	12	44	8	28
			A	15	35	—	—	10	32	—	—	8	32
			P	15	43	—	—	16	42	—	—	11	24
			T	15	45	—	—	14	32	—	—	10	28
49 (F)	19	34	S	10	10	—	—	12	20	—	—	8	18
			A	5	15	10	35	8	16	—	—	8	18
			P	0	0	5	10	0	0	0	0	0	0
50 (F)	44	6	G	7	30	—	—	8	25	—	—	8	28

some cases, angio-neurotic oedema and bronchospasm (Clarke et al., 1975; Leynadier, Luce and Dry, 1984; Vervloet, 1985). Each had been tested for anaphylaxis in this department by IST (first test) 2–57 months previously when they were found to have a positive IST to at least one of the drugs used during the anaesthetic (table II). Their informed consent was obtained for a further test—this time using IST and prick-tests. Four of the patients had been anaesthetized subsequent to the first test without experiencing anaphylaxis.

Group 2. Seven patients (table I) were tested for the first time after experiencing an anaphylactic reaction during anaesthesia.

Group 3. Six patients (table I) suffered a non-anaphylactic reaction during anaesthesia, such as isolated bronchospasm (two patients) or an anaphylactoid reaction to drugs other than those administered during general anaesthesia—such as blood components (one patient) or macromolecules (three patients). They had been tested by IST to anaesthetic agents 11–33 months previously and were found to have negative responses to the drugs studied on the present occasion.

Group 4. Sixteen subjects (members of the hospital staff) acted as controls (table I). Twelve had been anaesthetized without evident complication.

Materials

The administration of any drug known to modify the skin tests was stopped at least 48 h before the study was undertaken.

IST were undertaken using seven drugs that were available commercially (table II), diluted to 1 : 100 and 1 : 1000 in saline with phenol at a concentration of 0.5% (Chaix et Du Marais, 75011, Paris). The same saline solution was used as negative control; there were no positive controls. Fresh solutions of the drugs were prepared each month and were stored at 4 °C until required for injection—0.05 ml of each solution i.d. on the ventral surface of both arms between the elbow and shoulder, always in the same order, with four IST on each arm. The largest diameter of weal and flare was measured 20 min later. If there was a negative result with the 1 : 1000 concentration (which was used first), a second test was made with the 1 : 100 strength.

Prick tests were performed on each forearm, always in the same order, but remote from the elbow and wrist. The needles used were pre-charged with the same commercially-available drugs mixed with methylcellulose jelly and applied to a disposable single point device (fig. 1) (Stallerpoint, Laboratoire des Stallergènes, 160 quai Polangis, 94340 Joinville le Pont, France). The conical point of this device is 1 mm long and has four inset microcuvettes that facilitate the transcutaneous penetration of the test and control solutions (fig. 1). Negative controls were performed using the same jelly (without drug). Positive controls were obtained using histamine 1 mg ml^{-1}.

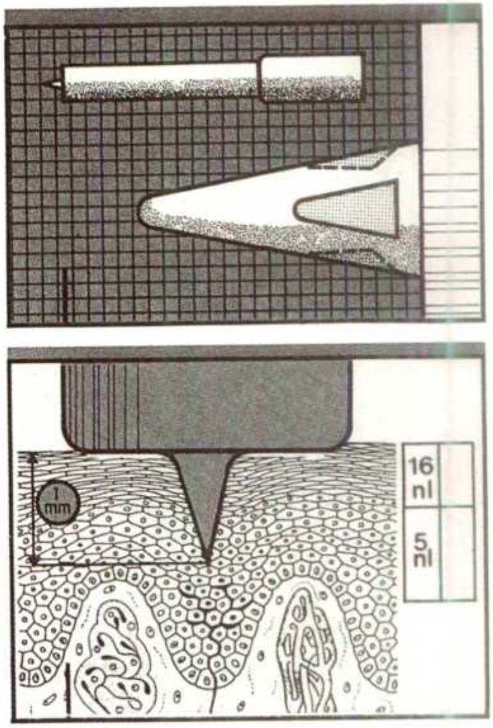

FIG. 1. Characteristics of the disposable single point used for prick tests.

RESULTS

Both prick tests and IST were considered positive when the weal was 5 mm or more and the flare 10 mm or more. No false positive or negative results were observed with control tests for both prick tests and IST.

Modification of IST with time (group 1) (table II)

Some of the drugs used in the present study had been tested previously and, for these drugs, the results of 301 out of 344 IST (87.5%) remained the same as previously (220 negative and 81 positive); of the 43 which changed, eight became positive (2.3%) and 35 became negative (10.2%). Thus of 116 IST originally positive, 35 (30.2%) became negative at second testing. With pancuronium, nine of 19 positive tests became negative (47.4%). There was no clear relationship with time.

Correlation between prick tests and IST (groups 1, 2 and 3)

Table III compares 441 tests and it can be seen that the results for prick tests and IST were in agreement in 426 out of 441 instances (96.6%;

TABLE III. *Comparisons of 441 results from prick tests (PT) and intradermal skin tests (IST (dilution 1 : 1000 followed, only if negative, by dilution 1 : 100)) in groups 1, 2 and 3 combined. Values represent number of tests in each category. Key to drugs as in table I*

	S	G	A	P	V	F	T	Total
PT and IST agree ($n = 426$):								
PT negative IST 1:1000 negative IST 1:100 negative	35	32	45	52	48	60	57	329
PT positive IST 1:1000 positive	19	22	13	9	11	2	4	80
PT positive (IST 1:1000 negative) IST 1:100 positive	7	4	4	1	1	0	0	17
PT and IST do not agree ($n = 15$):								
PT positive IST 1:1000 negative IST 1:100 negative	0	0	0	0	0	0	1	1
PT negative IST 1:1000 positive	2	1	0	1	2	1	1	8
PT negative (IST 1:1000 negative IST 1:100 positive	0	4	1	0	1	0	0	6

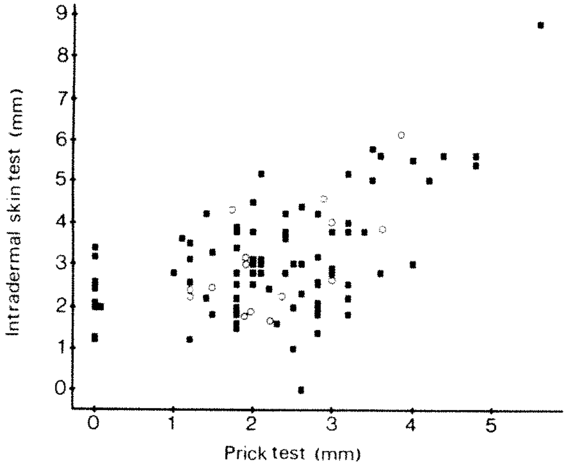

FIG. 2. Correlation ($r = 0.5$; $P < 0.001$) between diameters of weals obtained with prick tests and intradermal tests with drug concentrations of 1 : 1000 in group 1. Open circles represent intradermal skin tests positive only at 1 : 100 concentration (these results were not used in the calculation of correlation coefficients, but were excluded along with the negative results from both prick tests and IST).

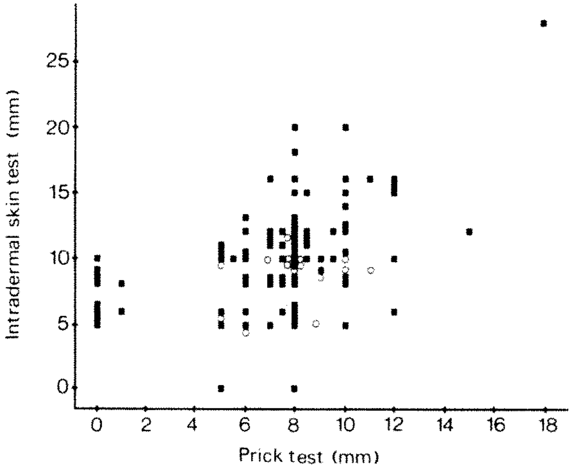

FIG. 3. Correlation ($r = 0.5$; $P < 0.001$) between diameters of flares obtained with prick tests and intradermal tests with drug concentrations of 1 : 1000 in group 1. Open circles represent intradermal skin tests positive only at 1 : 100 concentration (these results were not used in the calculation of correlation coefficients, but were excluded along with the negative results from both prick tests and IST).

$P < 0.001$). Discrepancies were mainly negative results with prick tests, particularly with gallamine. However, two out of four negative prick results with this drug were only weakly positive by IST with the 1 : 100 concentration.

On the other hand, the diameters of the weals with prick and IST correlated well in group 1 ($r = 0.5$; $P < 0.001$), as did the diameters of the flares ($r = 0.5$; $P < 0.001$) (figs 2, 3). For this calculation the negative results with both prick tests and IST were excluded.

All skin tests were negative in group 3.

Skin tests in control subjects (group 4)

All were negative, apart from one subject who had positive IST (1:1000) and prick test to fentanyl.

DISCUSSION

The value of skin tests has been well established in the diagnosis of anaphylaxis to anaesthetic agents (Fisher, 1979; Leynadier, Luce and Dry, 1984; Vervloet, 1985; Vervloet, Benzarti et al., 1985). Moreover, IST have been used to demonstrate the inhibiting effect of choline, which contains a quaternary ammonium group and acts as a monovalent hapten (Vervloet, Benzarti et al., 1985). However, IST are time consuming, sometimes difficult to perform by untrained operators and cannot be used systematically before general anaesthesia. Anaphylaxis is unpredictable and may occur even in patients who are anaesthetized for the first time (Clarke et al., 1975; Leynadier, Luce and Dry, 1984).

Prick tests are easy to perform, innocuous and used in the emergency diagnosis of allergy, in preference to IST.

We have included tests to five neuromuscular blocking drugs that are generally suspected of producing anaphylaxis, as well as two other drugs, fentanyl and thiopentone, which are frequently used in anaesthesia. Patients in groups 1 and 3 had been tested previously with some of these drugs and an unexpected variation of IST with time was seen. Skin tests became negative in 30.2% of instances. This result was not observed by Vervloet, Arnaud and colleagues (1985b), but they tested only suxamethonium. There was no clear relationship between these results and the time which had elapsed between the tests. It is possible that IgE antibodies specific to anaesthetics, particularly to pancuronium, have the same unpredictable half-lives as those of IgE specific to penicillin (from 10 to more than 1000 days) (Adkinson, 1984). These results emphasize that, if skin tests are to have a predictive value, they must be performed just before each anaesthetic.

There was a significant correlation between the prick tests and the IST (97.3%; $P < 0.001$ for 553 tests) and the diameters of reactions to the two kinds of skin test showed significant correlation. The discrepancies observed were mostly with gallamine and were, in part, the result of a lower sensitivity of the prick tests. A higher concentration of this drug than that which was used in the present study would be necessary to elicit positive results. However, it is difficult to interpret the weak positive results of IST that were observed in four patients with negative prick tests. One explanation is that IST are more sensitive but less specific and probably less reliable than prick tests in assessment of immediate hypersensitivity.

In conclusion, anaphylaxis to anaesthetic agents represents one of the most serious side-effects of drugs. Its frequency may possibly be reduced by the detection of allergic patients by means of prick tests. These tests may satisfy the assertion of Watkins, Wild and Clarke, (1985): "any simple test predictive of immediate hypersensitivity-like (anaphylactoid) response to anaesthetic agents would be clinically useful".

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CAN CLINICAL ANAPHYLAXIS TO ANAESTHETIC DRUGS BE PREDICTED FROM ALLERGIC HISTORY?

M. McD. FISHER, A. OUTHRED AND C. J. BOWEY

SUMMARY

The incidence of a history of allergy, atopy or asthma is greater in patients who undergo life-threatening clinical anaphylaxis to anaesthetic drugs. However, because the incidence is low, the presence of such a history is not a reliable predictor of the likelihood of a reaction in an individual patient, and does not indicate that the patient should be investigated or pretreated, or that the selection of drug(s) be altered to reduce the likelihood of a reaction.

All studies which have compared the incidence of a history of allergy, atopy or asthma in patients experiencing severe clinical anaphylaxis during anaesthesia, with the incidence in non-reacting patients have shown a statistically significant increase in the incidence of these disorders in the reacting patients (Dundee et al., 1978; LaForest, More and Fisher, 1980; Laxenaire et al., 1982; Galletly and Treuren, 1985). This has led some authors to postulate that, in such patients, the selection of drugs for anaesthesia should be altered in the light of the patient's history (Clarke, Fee and Dundee, 1978; Watkins, Clarke and Fee, 1981), or that the patient should be pre-treated with an antihistamine (Lorenz, 1985)—with the implication that such management will reduce the risk of adverse reactions.

These hypotheses appear to have taken on medico-legal significance and it is a common item of complaint, when patients seek legal redress against the anaesthetist who has administered the drug which caused a severe reaction, that inappropriate drugs were given or that inappropriate investigations were performed before operation in the light of the patient's history of allergy, atopy or asthma.

If a history of these diseases indicates that action by the anaesthetist could reduce the recurrence of severe clinical anaphylaxis, then these diseases can be considered as predictive tests and their value as such assessed.

PATIENTS AND METHODS

One thousand patients who underwent uneventful anaesthetics at the Royal North Shore Hospital of Sydney were questioned before operation, by the anaesthetist, as to the presence of allergy, atopy or asthma. The results have been published previously (LaForest, More and Fisher, 1980). Two hundred and twenty-seven patients who had life-threatening clinical anaphylaxis during anaesthesia—as judged by previously published criteria (Fisher and Munro, 1983)—were questioned following the reaction for a history of allergy, atopy or asthma before the reaction. In the case of seven non-survivors their hospital records were perused.

The methodologies of Galen and Gambino (1975) and of Cox (1984) were used to evaluate the indices of a history of allergy, atopy or asthma as diagnostic tests for their likelihood of predicting a life-threatening clinical anaphylactic reaction. The reported incidence of such reactions is between 1:600 (Vervloet, 1985) and 1:20000 (Fisher and Baldo, 1984). The Boston Collaborative Drug Surveillance Survey estimated the rate of reactions as 1:4395 anaesthetics with 90% confidence limits of 1:980–1:200000 (Beard and Jick, 1985). The indices were evaluated using a population constructed for incidence of 1:500–1:20000 using the reacting and non-reacting populations.

The methodology (Galen and Gambino, 1975;

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TABLE I. *Percent of reactors and non-reactors with history of allergy, atopy and asthma in selected populations*

	Australia		New Zealand		France		United Kingdom	
	Reactor	Non-reactor	Reactor	Non-reactor	Reactor	Non-reactor	Reactor	Non-reactor
n	227	1000	42	200	100	—	100	10000
Allergy (%)	45	14.9	53	14	8.16	3.7	29	13.5
Atopy (%)	33	8.5	26	7	31	14	14	8.5
Both (%)	23.8	6.2	—	—	—	—	4	3.1
Asthma (%)	18.9	4.1	—	—	—	—	—	3.6

Cox, 1984) involves calculating the probabilities that the test (allergy, atopy or asthma) is significantly related to the disease. A 2×2 table is constructed, setting out whether the test is positive or negative in patients with or without the disease:

	Disease present	Disease absent
Test positive	*a*	*b*
Test negative	*c*	*d*

The following may then be derived:

Sensitivity (true positive rate) $= \frac{a}{a+c}$
Specificity (true negative rate) $= \frac{d}{b+d}$
Positive predictive value $= \frac{a}{a+b}$
Negative predictive value $= \frac{d}{c+d}$
False alarm rate $= \frac{b}{a+b}$
False reassurance rate $= \frac{c}{c+d}$

We constructed populations from the Australian data to give a prevalence of severe anaphylactoid reactions of 1:500 and 1:20000 and evaluated allergy, atopy and asthma as predictive tests for life-threatening reactions.

RESULTS

The incidence of a history of allergy, atopy, asthma or both in the Australian population is shown in table I, and the figures for British (Dundee et al., 1978), French (Laxenaire et al., 1982) and New Zealand (Galletly and Treuren, 1985) populations are included for comparison.

In the Australian population there was a statistically significant increase in the incidence of a history of allergy, atopy or asthma in patients who reacted to anaesthetic drugs, compared with patients who underwent uneventful anaesthesia (table II).

Table III shows the sensitivity, specificity, predictive values, false alarm and false reassurance

TABLE II. *Difference incidence of allergy, atopy and asthma in reacting and non-reacting populations*

	Reactors	Non-reactors	*P*
n	227	1000	
Allergy	101	149	> 0.999
Atopy	75	85	> 0.999
Both	54	64	> 0.999
Asthma	43	41	> 0.999

TABLE III. *Value of a history of allergy, atopy or asthma in prediction of risk of clinical anaphylaxis during anaesthesia*

	Incidence 1:500				Incidence 1:20000			
	Allergy	Atopy	Both	Asthma	Allergy	Atopy	Both	Asthma
Sensitivity (%)	44.9	33.04	23.79	18.91	44.9	33.04	23.79	18.91
Specificity (%)	85.1	91.5	93.6	95.9	85.1	91.5	93.6	95.9
Positive predictive value (%)	0.6	0.77	0.71	0.92	0.01	0.02	0.02	0.02
Negative predictive value (%)	99.9	99.9	99.9	99.9	1	1	1	1
False alarm rate (%)	99.7	99.6	99.6	99.5	99.99	99.98	99.98	99.98
False reassurance rate (%)	0.07	0.07	0.09	0.09	0	0	0	0

rates of a history of allergy, atopy and asthma as diagnostic tests for a reaction rate of 1:500 anaesthetics and for a reaction rate of 1:20 000 anaesthetics. The results show that such a history is not a valid predictor of the likelihood of a severe clinical anaphylactic reaction at the reported published incidences of life-threatening clinical anaphylaxis.

DISCUSSION

The figures in table III demonstrate that a history of allergy, atopy or asthma is not a reliable predictor of the risk of severe clinical anaphylaxis. Although specificity (the likelihood that a negative finding will occur in a patient without the disease) is high, all other indices of the effectiveness of such a history as a predictor are unacceptable. Prevalence of the disease is probably the most important variable (Cox, 1984) affecting the predictive value of diagnostic tests, and table III shows that the predictive value of an "allergic" history is poor for all published ranges of incidence.

Further, the potential interventions based on such a history have not been validated. Choice of low-risk drugs and pretreatment have both been subject to failure with fatal consequences (Watkins, 1985), and preoperative intradermal testing does not appear a valid predictor in the absence of a past history of a reaction (Fisher, 1985; Wood et al., 1985).

This is not to say that care should not be taken with potent histamine-releasing drugs in patients with an allergic or atopic history, as there is evidence that the direct histamine-releasing effects of drugs may be more pronounced in patients with such a history (Laxenaire et al., 1982), or in patients with cardiovascular disease (Philbin et al., 1981). If these drugs are indicated in such patients, their direct histamine-releasing effects can be reduced by slow injection and blocked by the administration of H_1- and H_2-receptor blocking drugs (Lorenz, 1985). The situation with respect to a history of asthma is less clear since, although *in vitro* tests of blood from asthmatic and non-asthmatic patients show greater histamine release in asthmatics (Guldager et al., 1985), and atopic patients are sensitive to histamine (Laxenaire et al., 1982), the only factor proven to be likely to make asthma worse during clinical anaesthesia is the placement of a tracheal tube (Schnider and Papper, 1961). The occurrence of life-threatening clinical anaphylaxis does not appear to be related to the ability of drugs to release histamine (Fisher and Baldo, 1984).

Thus modification in anaesthetic technique based on a history of allergy, atopy or asthma is unlikely to reduce the likelihood of severe clinical anaphylaxis.

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HARMLESS CUTANEOUS REACTIONS ASSOCIATED WITH THE USE OF ATRACURIUM

A Report of 1200 Anaesthetics

D. E. ROWLANDS

SUMMARY

One hundred and fifty-one cutaneous reactions occurred during 1200 anaesthetics in which atracurium was given. The majority occurred in females less than 70 years old. Bronchospasm and serious hypotension did not occur, and it is concluded that a history of allergic response or asthma is not a contraindication to the use of atracurium.

In view of reports of the histamine-releasing potential of atracurium (Basta et al., 1983; Scott et al., 1985), and of cutaneous reactions associated with its use (Coleman, Hunter and Hunt, 1983; Nightinghale and Bush, 1983; Lavery and Mirakhur, 1984; Mirakhur et al., 1985), the anaesthetic records of 1200 patients to whom atracurium had been given were examined in an attempt to assess the clinical significance of these findings.

PATIENTS AND METHODS

Atracurium was given by the author on 1200 occasions to 1123 patients, aged between 4 and 91 yr, undergoing elective or emergency operations requiring the use of a neuromuscular blocking drug as part of the anaesthetic regimen. The study began 21 months before the issue of a product licence in the U.K. (Rowlands, 1983).

Three hundred and twelve patients received no premedication, 722 were given diazepam 5–10 mg by mouth, 78 received lorazepam 2.5–5 mg by mouth; the remainder received other premedicants. Anaesthesia was induced with methohexitone 1.1–1.7 mg kg^{-1} i.v. (to which lignocaine had been added to reduce the frequency of pain during the injection (Rowlands, 1969)) given over 20–85 s. Atracurium 0.3–0.6 mg kg^{-1} was then given through the same 27-gauge (12 × 0.4-mm) needle over 5–10 s.

The drugs were injected to a vein on the dorsum of the hand in approximately three-quarters of the patients, and to a vein in the antecubital fossa in most of the remainder.

In 62 patients droperidol 5–10 mg and fentanyl 0.1–0.2 mg were administered i.v. before the methohexitone and atracurium. On 150 occasions a priming dose of atracurium 2.5 or 5.0 mg was given to the patient 2–3 min before the induction of anaesthesia (Foldes, 1984).

Arterial pressure was recorded by sphygmomanometry immediately before the induction of anaesthesia, between 3 and 7 min later and then at regular 7.5-min intervals. A 10% decrease (or greater) in systolic arterial pressure from the pre-anaesthetic value was regarded as evidence of "hypotension".

Initially, cutaneous reactions were noted when they occurred (group 1; $n = 400$ administrations of atracurium). Following reports of reactions they were sought more actively (group 2; $n = 800$).

RESULTS

Details of the doses of atracurium, the sexes and mean ages of the 151 patients in whom a transient cutaneous reaction occurred are given in table I, and the distribution between groups 1 and 2 in table II.

Twenty-five of the 106 who gave a previous history of allergy showed a cutaneous reaction. No reactions developed in the 17 patients with history of asthma. The reactions occurred within

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TABLE I. *Cutaneous reactions to atracurium in 1200 anaesthetics (151 reactions occurred: 13%)*

	Female		Male	
Dose	< 70 yr	> 70 yr	< 70 yr	> 70 yr
0.3–0.39 mg kg^{-1}	31 in 131 (24%)	1 in 29 (3%)	8 in 69 (12%)	0 in 10 —
0.5–0.6 mg kg^{-1}	90 in 414 (22%)	4 in 148 (3%)	15 in 216 (7%)	2 in 183 (1%)
Total	121 in 545 (22%)	5 in 177 (3%)	23 in 285 (8%)	2 in 193 (1%)

TABLE II. *Cutaneous reactions to atracurium in groups 1 and 2 (151 reactions occurred: 13%) (For details of groups see text)*

	Female		Male	
Dose	< 70 yr	> 70 yr	< 70 yr	> 70 yr
Group 1 (1–400)	19 in 208 (9%)	0 in 55 —	1 in 76 (1%)	0 in 61 —
Group 2 (401–1200)	102 in 337 (30%)	5 in 122 (4%)	22 in 209 (11%)	2 in 132 (1.5%)
All	121 in 545 (22%)	5 in 177 (3%)	23 in 285 (8%)	2 in 193 (1%)

0.5–6 min after the initial dose of atracurium. One patient developed four weals on the trunk at 6 min, the largest being 1.7 × 1.2 cm, one of which (1.0 × 0.5 cm) was still present at the end of the operation 50 min later. The remainder of the reactions varied from a slight redness to generalized flushing of the chest or neck, and occasionally of the face, abdomen and limbs. On 22 occasions there was redness or a solitary weal (twice) at the injection site or for a small distance along the injection vein in addition to the truncal rash, and on seven occasions the injection site or vein alone were affected. No generalized urticaria occurred. Two of the rashes lasted for 30 min, one for 17 min; the remainder were fading or had cleared within 5 min.

The incidence of reactions was not reduced by the administration of a priming dose, and one occurred after atracurium 5 mg (0.08 mg kg^{-1}) before the methohexitone had been given. No reactions occurred with incremental doses.

Three patients with cutaneous reactions developed hypotension. In one patient, the systolic pressure decreased from 115 to 60 mm Hg at 3 min and returned to the pre-anaesthetic value within 1 min. In two other patients there were transient decreases of between 10 and 15% of the pre-anaesthetic value. There was no cause for anxiety in any of the patients who developed cutaneous reactions, nor was any treatment given.

Blood samples from the first of these patients were sent to the National Adverse Anaesthetic Reaction Advisory Service at Sheffield for investigation (Watkins, Thornton and Clarke, 1976). The report suggested that this was a "harmless reaction involving some anxiety of the patient and perhaps an underlying immunopathology following a viral infection".

Three patients developed a cutaneous reaction on their first anaesthetic with atracurium but not on their second, and two patients developed a reaction during their second anaesthetic, having shown no reaction during their first anaesthetic.

Two cases of bronchospasm occurred in asthmatic patients in whom intubation was attempted prematurely before the atracurium had taken full effect; there were no problems with incremental doses in these patients.

DISCUSSION

The lower incidence of reactions in group 1 (table II) may be because some minor or transient rashes were not detected. Table I suggests that the incidence in the dose range 0.3–0.6 mg kg^{-1} was not dose-related, and both tables show that cutaneous reactions occurred mainly in female patients younger than 70 yr.

Nightingale and Bush (1983) reported a local histamine-like response around the injection vein after atracurium in most of 154 children in whom anaesthesia was induced with thiopentone and who were given atracurium into a different vein in the palmar surface of the wrist. Lavery and Mirakhur (1984) reported a higher incidence of reactions in children who were given thiopentone–atracurium (13 in 33) than in those given atracurium without thiopentone (three in 17) (the i.v. details were not given).

Coleman, Hunter and Hunt (1983) reported a 25% incidence of skin reactions (including 8% urticaria) in 64 patients using thiopentone and atracurium through the same needle, with two examples of bronchospasm (one of questionable clinical significance).

Mirakhur and his colleagues (1985) found a dose-dependent cutaneous flushing in five groups of 40 patients: 17% when using 0.4 mg kg^{-1}, 32.5% with 0.5 and 0.6 mg kg^{-1}, reaching 55% at 0.75 mg kg^{-1} and 72.5% at 1.0 mg kg^{-1}, with one example of bronchospasm and hypotension at the highest dose. The latter two doses are considerably greater than those used normally in clinical practice, and it is not stated how the drugs were given.

From these reports and from the one patient in this series who developed a rash after atracurium 5 mg, it appears that atracurium alone can cause a cutaneous reaction, but that this is much more likely when the drug is given through the same needle as thiopentone.

The data in group 2 may give a more accurate indication of the incidence of cutaneous reactions than those of the whole series. The 16% incidence in 800 anaesthetics is decreased by the presence of 32% of elderly patients who have few reactions, while the 23% incidence in the 546 patients younger than 70 years is increased by the presence of 62% female patients, who have many. Direct comparison with other studies is difficult as the sex of their patients with reactions is not given, but it is probable that the incidence of reactions in this series is lower than in those mentioned above.

The occurrence of transient hypotension in three patients with rashes may have been attributable to methohexitone.

Hughes (1985) suggested that local reactions could be minimized if the induction agents and atracurium were injected to the vein through a fast flowing infusion, and if their administration was separated by an interval of about 30 s. Watkins (1986) suggested that the mixing and precipitation which occurs between the thiopentone and atracurium injected through the same indwelling cannula may initiate systemic aggregate anaphylaxis and potentially life-threatening bronchospasm. Sale (1983) reported a patient with bronchospasm as well as erythema and weal along the line of the vein into which thiopentone and atracurium had been given through a 21-guage Butterfly needle.

Methohexitone is generally regarded as causing fewer allergic responses than thiopentone; furthermore, a random test indicated that the 1% methohexitone–lignocaine solution used for induction in this series was less alkaline (pH 12.8) than 2.5% thiopentone (pH 14). However, the lower onset of cutaneous reactions and the absence of urticaria, bronchospasm and serious hypotension in this series could be the result of the smaller interface available between the two drugs for reactions to occur when they are given through a small (12 × 0.4-mm) needle rather than through a large needle or Butterfly needle, where mixing can take place more readily.

Slow (75 s) injection of atracurium may reduce histamine release (Scott et al., 1985), and the incidence of cutaneous reactions could possibly be reduced by an injection time slower than the 5–10 s taken in the present study. The incidence of cutaneous reactions in this series was not decreased by a priming dose as suggested by Foldes (1984). A cutaneous reaction was not regarded as a contraindication to the further use of atracurium in view of the blood samples of the patient in whom the first reaction occurred and the fact that no reactions occurred with incremental doses in any patient.

Galletly and Treuren (1985) have found the female sex to be a predisposing factor to sensitivity to neuromuscular blockers—cutaneous reactions occurred mainly in females younger than 70 yr in this series.

An allergic reaction to atracurium has been reported by Aldrete (1985) who gave 0.6 mg kg^{-1} rapidly followed by thiopentone 4 mg kg^{-1}. A severe cutaneous reaction occurred as well as a slight increased resistance to ventilation. Skin testing 24 h later gave a positive reaction to atracurium. However, the findings of my series support the statement by Watkins (1986) that, in clinical terms, atracurium emerges as a safe drug with useful neuromuscular blocking properties, but with an irritating tendency to produce predominantly harmless cutaneous manifestations. Provided due care is taken to avoid mixing of drugs, atracurium may be used in patients with a history of asthma or allergic reactions.

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PHARMACOKINETICS OF ATRACURIUM AND ITS METABOLITES IN PATIENTS WITH NORMAL RENAL FUNCTION, AND IN PATIENTS IN RENAL FAILURE

S. WARD, N. BOHEIMER, B. C. WEATHERLEY, R. J. SIMMONDS AND T. A. DOPSON

Atracurium is a non-depolarizing neuromuscular blocking agent with an intermediate duration of action. Recovery of neuromuscular function following an i.v. bolus dose is determined by the pharmacokinetic elimination (β-phase) half-life of 20 min, rather than the redistribution (α-phase) half-life of 2 min (Ward and Wright, 1983). Elimination is unique, among this group of drugs, as it is caused by a combination of chemical and enzyme-mediated hydrolysis, and the pH and temperature-dependent "Hofmann" destruction of the bis-quaternary molecule to yield various metabolites (fig. 1) (Stenlake et al., 1983). This study was in two parts. First, the pharmacokinetic profile of atracurium itself was determined in patients with renal failure and, second, the pharmacokinetic profiles of two of its metabolites were determined in patients with normal renal function, and in patients in chronic renal failure.

SUMMARY

The plasma pharmacokinetic profiles of atracurium and its derivatives, laudanosine and monoquaternary alcohol, were studied in six patients with renal failure after a bolus dose of atracurium 0.3–0.4 mg kg^{-1}. The pharmacokinetics of the derivatives only were studied in a group of four normal patients receiving atracurium 0.3 mg kg^{-1}. Measurements of plasma and urine concentrations were performed by high pressure liquid chromatography. Pharmacokinetics of atracurium were not significantly different in the renal failure group when compared with those obtained in a previous study on six normal patients. Although 2–10% of the dose was recovered in the urine of normal patients as unchanged atracurium, and 3–4% as laudanosine, renal failure produced no significant differences in plasma pharmacokinetics, with mean plasma elimination half-lives of 20 min for atracurium, 234 min for laudanosine and 39 min for quaternary alcohol.

PATIENTS AND METHODS

Patients

Ten patients gave written consent to be included in this study. Four of the patients (group I) were female (ASA I) patients undergoing laparoscopic sterilization. Six of the patients (group II) were in chronic renal failure; all were anuric and required regular haemodialysis, and were undergoing various surgical procedures (table I) none of which lasted longer than 30 min. Each patient was assessed before surgery, and temazepam 30 mg was given orally at least 90 min before the induction of anaesthesia. Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and maintained with 66% nitrous oxide and 0.8% enflurane in oxygen. Ventilation was controlled and physiological tensions of carbon dioxide maintained by measuring end-tidal values. Tracheal intubation was performed after adequate relaxation had been obtained (atracurium

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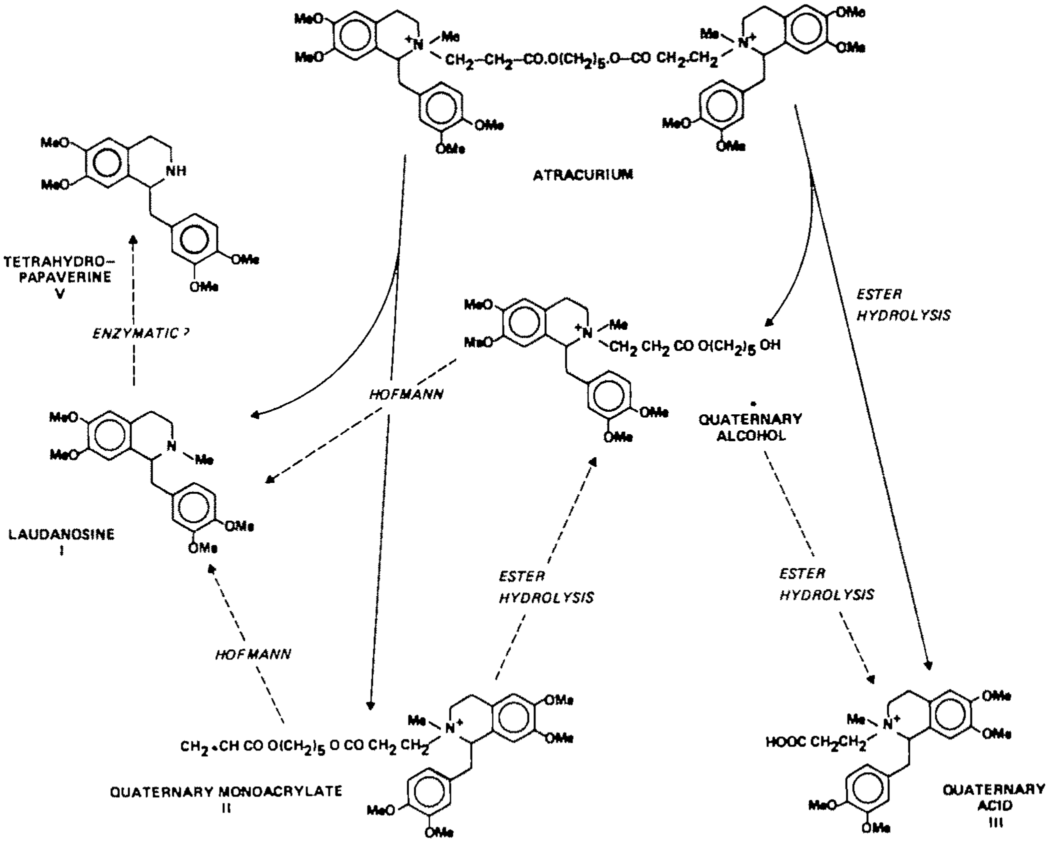

FIG. 1. Postulated breakdown for atracurium and its derivatives.

0.3–0.4 mg kg^{-1}) and the cords had been sprayed (4% lignocaine). Neuromuscular function was monitored in all of the patients in group I, and four of the six patients in group II, by analysis of the compound EMG in the hypothenar muscles following supramaximal train-of-four stimuli to the ulnar nerve in the forearm via surface electrodes (Relaxograph, Datex). Neuromuscular function was allowed to recover spontaneously in every patient. Two veins were cannulated: one in a forearm for drug administration, the other in the opposite arm for blood sampling. Arterial pressure and the ECG were recorded throughout. Before the administration of atracurium, and at regular intervals thereafter (0, 2, 5, 10, 20, 30, 45, 60, 100, 200, 300, 400 and 500 min), 5-ml samples of heparinized blood were obtained (but not at 20 and 45 min from normal group I). Each sample was centrifuged rapidly and the plasma separated, acidified and stored in duplicate at −20 °C within 2 min. From three of the normal patients (group I) urine was collected for analysis up to 500 min. Each of these patients had voided their bladder before the induction of anaesthesia.

TABLE I. *Clinical data for patients in chronic renal failure*

Patient No.	Age (yr)	Sex	Wt (kg)	Atracurium (ng kg^{-1})	Operation
1	21	M	79	0.3	Excision abscess
2	52	F	53	0.4	Splenectomy
3	54	M	66	0.3	A.V. fistula
4	23	F	52	0.3	Tenchkoff insertion
5	65	F	59	0.3	Tenchkoff insertion
6	59	M	71.5	0.3	Debridement ankle ulcer

Analytical technique

The published method for the analysis of atracurium in human plasma (Neill and Jones, 1983), was not suitable for the measurement of the monoquaternary metabolites, and a new HPLC method was devised (Simmonds, 1985). Briefly, the acidified plasma samples were spiked with N-methyl laudanosine as internal standard, and passed through a primed "Bond Elut" phenyl cartridge, where atracurium and its derivatives were adsorbed. After washing, the components were eluted with a small volume of primary HPLC mobile phase and, after vacuum concentration, analysed on a strong cation exchange column with gradient elution using fluorescence detection. The recovery of components was greater than 95%, and the limit of detection was 10 ng ml^{-1} for atracurium, laudanosine and monoquaternary alcohol. If the extracts were analysed within 3 days of production, the coefficient of variation was below 10% over the range 100–5000 ng ml^{-1}.

Calculations

In group II (renal failure patients) the atracurium plasma data were fitted to a two-compartment model by the method of non-linear least squares analysis (Metzler, Elfring and McEwen, 1974), and the distribution half-life ($T_{\frac{1}{2}}^{\alpha}$), the elimination half-life ($T_{\frac{1}{2}}^{\beta}$), the volume of the central compartment (V_1), the volume of distribution (V^{β}) and the total clearance (Cl) were determined. The values found were compared, using standard statistical software (Dixon, 1983), with those from a previous study of normal patients (Ward et al., 1983) given a similar dose.

The renal clearances of atracurium in three of the normal patients were determined by dividing the total amount of atracurium recovered in the urine, by the trapezoidal area under the plasma atracurium curve up to 500 min after its administration.

For the two atracurium derivatives, a standard two-compartment model with first order input from the atracurium plasma compartment was assumed (fig. 2), with the atracurium plasma profile being calculated from the mean dose-normalized atracurium macroscopic kinetic parameters in the literature (Weatherley, Williams and Neill, 1983) ($A = 18.7\ \mu\mathrm{g\ ml^{-1}\ mg^{-1}\ kg^{-1}}$; $B = 4.9\ \mu\mathrm{g\ ml^{-1}\ mg^{-1}\ kg^{-1}}$; $T_{\frac{1}{2}}^{\alpha} = 2.2$ min; $T_{\frac{1}{2}}^{\beta} = 20.0$ min).

A computer package (Chance et al., 1977), was used to provide unweighted least squares estimates of the pharmacokinetic parameters for laudanosine, and log-weighted estimates for monoquaternary alcohol. Apparent clearances, Cl_{app} were defined as the dose of atracurium administered

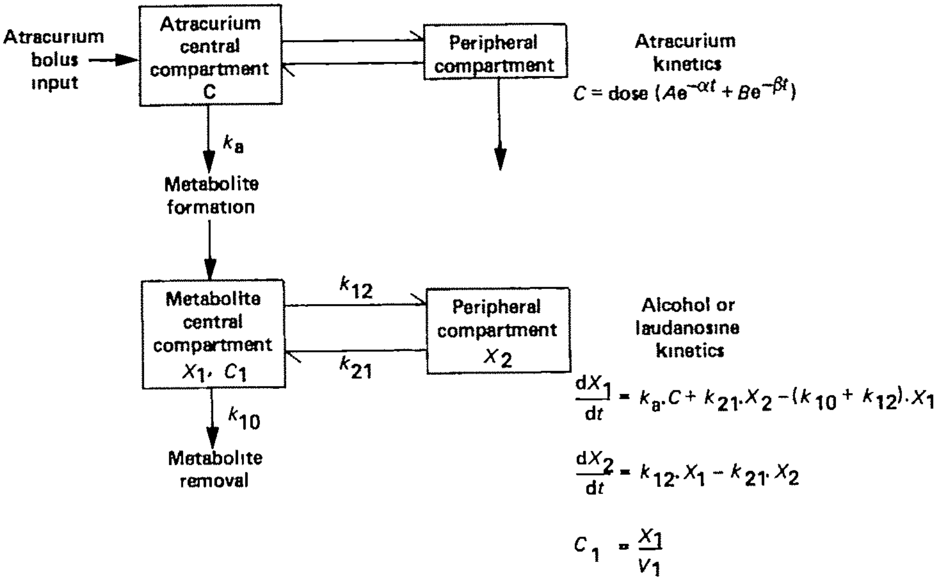
Atracurium bolus input
Atracurium central compartment
C
Peripheral compartment
Atracurium kinetics
$C = \mathrm{dose}\ (Ae^{-\alpha t} + Be^{-\beta t})$
k_a
Metabolite formation
Metabolite central compartment
X_1, C_1
k_{12}
k_{21}
Peripheral compartment
X_2
Alcohol or laudanosine kinetics
$\frac{dX_1}{dt} = k_a . C + k_{21} . X_2 - (k_{10} + k_{12}) . X_1$
$\frac{dX_2}{dt} = k_{12} . X_1 - k_{21} . X_2$
$C_1 = \frac{X_1}{V_1}$
k_{10}
Metabolite removal

FIG. 2. Pharmacokinetic model for laudanosine or monoquaternary alcohol. X_1, X_2 = amounts of metabolite in its central (plasma) and peripheral compartments respectively; C_1 = metabolite concentration in the plasma compartment of volume V_1. k_{12}, k_{21} = exchange rate constants; k_a = formation rate constant of metabolite from atracurium in the atracurium central (plasma) compartment. Atracurium concentrations were calculated from the dose and values A, B, α, and β given in the literature (Weatherley, Williams and Neill, 1983). k_a was set equal to β, and V_1, k_{10}, k_{12}, k_{21} were estimated by unweighted least squares fitting to the laudanosine plasma concentrations and to the logarithms of the monoquaternary alcohol plasma concentrations, using a general computer package (Chance et al., 1977), to model the differential equations.

TABLE II. *Atracurium pharmacokinetic values for patients with chronic renal failure*

	Patient No.						
	1	2	3	4	5	6	Mean ± SEM
$T_{\frac{1}{2}}^{\alpha}$ (min)	6.0	5.2	2.9	2.6	2.2	2.7	3.60 ± 0.65
$T_{\frac{1}{2}}^{\beta}$ (min)	22.1	24.6	20.3	18.7	13.3	21.4	20.1 ± 1.6
Cl (ml min^{-1} kg^{-1})	3.3	8.7	4.6	7.2	7.0	4.0	5.8 ± 0.9
V_1 (ml kg^{-1})	53	114	48	109	87	70	80 ± 11
V^{β} (ml kg^{-1})	93	196	126	189	126	115	141 ± 17

divided by the area under the derived plasma concentration curve from time zero to infinity.

Steady state plasma concentrations were calculated for each patient by dividing the maximum recommended infusion rate of atracurium expected to achieve > 95 % neuromuscular blockade (0.6 mg kg^{-1} h^{-1}), by the apparent clearances (Cl_{app}). Maximum true urinary clearances were obtained by dividing the total amount of derivative recovered in urine by the trapezoidal area under the derivative plasma curve from time zero to 500 min.

The results were compared, for all pharmacokinetic variables, between patients with and without renal function using the appropriate Student's t test, after performing tests on the

TABLE III. *Comparison of atracurium pharmacokinetic values between normal patients and patients with chronic renal failure.* **V^{β} referred to as* V*area by Ward and co-workers (1983). This reference is the source of the Normal column*

	Normal (mean ± SEM) (n = 6)	Renal failure (mean ± SEM) (n = 6)	Variance test	t Test
Dose (mg kg^{-1})	0.3	0.3–0.4		
$T_{\frac{1}{2}}^{\alpha}$ (min)	2.27 ± 0.31	3.60 ± 0.65	$P < 0.05$	ns
$T_{\frac{1}{2}}^{\beta}$ (min)	19.3 ± 0.9	20.1 ± 1.6	ns	ns
Cl (ml min^{-1} kg^{-1})	5.5 ± 0.3	5.8 ± 0.9	$P < 0.01$	ns
V_1 (ml kg^{-1})	55 ± 8	80 ± 11	ns	ns
V^{β} (ml kg^{-1})*	153 ± 13	141 ± 17	ns	ns

TABLE IV. *Maximum plasma concentrations* (μg ml^{-1}) *of atracurium derivatives (mean ± SD)*

	Normal (n = 4)	Renal failure (n = 6)	Variance test	t Test
Laudanosine	0.19 ± 0.04	0.27 ± 0.10	$P < 0.05$	ns
Range	0.14–0.24	0.14–0.37		
Monoquaternary alcohol	0.49 ± 0.07	0.43 ± 0.16 (n = 5)	$P < 0.05$	ns
Range	0.43–0.58	0.24–0.62		

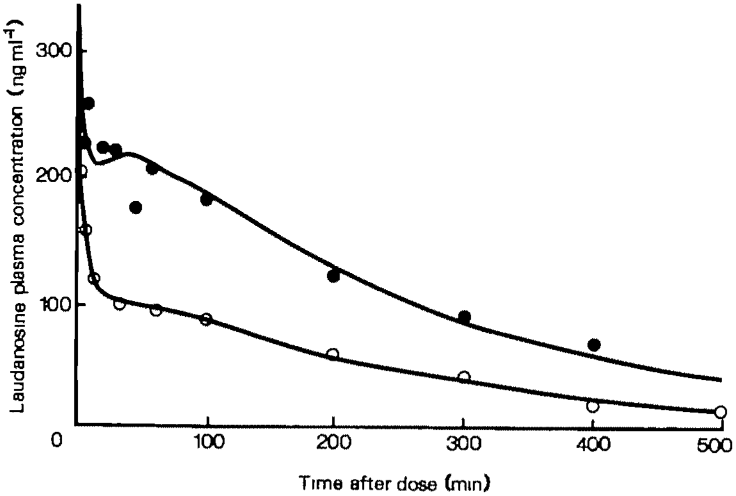

FIG. 3. Plasma concentrations of laudanosine in a selected (for clarity of presentation) normal (○) and renal failure patient (●) after a 0.3-mg kg^{-1} i.v. bolus dose of atracurium. The solid lines are computer fitted (see text).

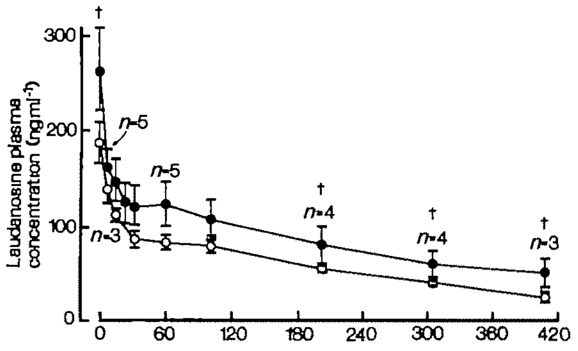

FIG. 4. Mean (±SEM) plasma concentrations of laudanosine in six (unless otherwise indicated) patients in renal failure (●) and four (unless otherwise indicated) normal patients (○) after a bolus of atracurium 0.3–0.4 mg kg^{-1}. †Variance significantly different (*F* test; $P < 0.05$).

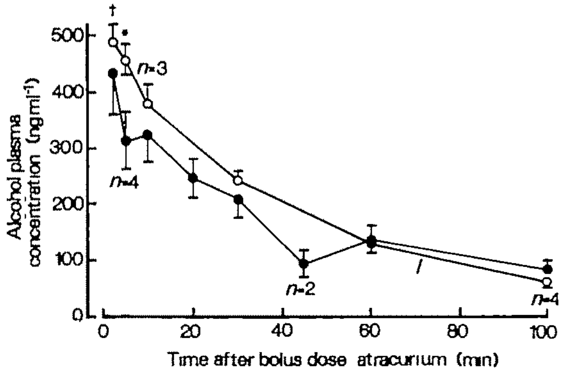

FIG. 6. Mean (±SEM) plasma concentrations of monoquaternary alcohol in five (unless otherwise indicated) patients in renal failure (●) and four (unless otherwise indicated) normal patients (○) after a bolus of atracurium 0.3–0.4 mg kg^{-1}. †Variance significantly different (*F* test, $P < 0.05$). *Mean significantly different (*t* test; $P < 0.05$).

variances (Levene, 1960). Differences were considered significant at the $P < 0.05$ level.

RESULTS

The atracurium pharmacokinetic variables in patients with renal failure (table II) were not significantly different from those in a group of normal patients (table III). The peak concentrations (for each metabolite), measured at 2 min after dosing, were unaffected by renal failure (table IV). Plasma concentrations of laudanosine reached their maxima at 2 min, decreased rapidly to plateau at around 0.1–0.2 µg ml^{-1} by 100 min and then decayed exponentially (figs 3, 4). A similar pattern was seen with the monoquaternary alcohol (figs 5, 6), which produced a plateau of 0.3–0.4 µg ml^{-1} at about 10 min, followed by a more rapid decay. The final elimination half-lives and derived apparent clearances of laudanosine and the monoquaternary alcohol were not significantly altered by renal failure (table V) and, therefore, predicted steady-state plasma concentrations of laudanosine and the monoquaternary alcohol (table VI), were not altered significantly by renal failure.

The urinary recoveries of atracurium and

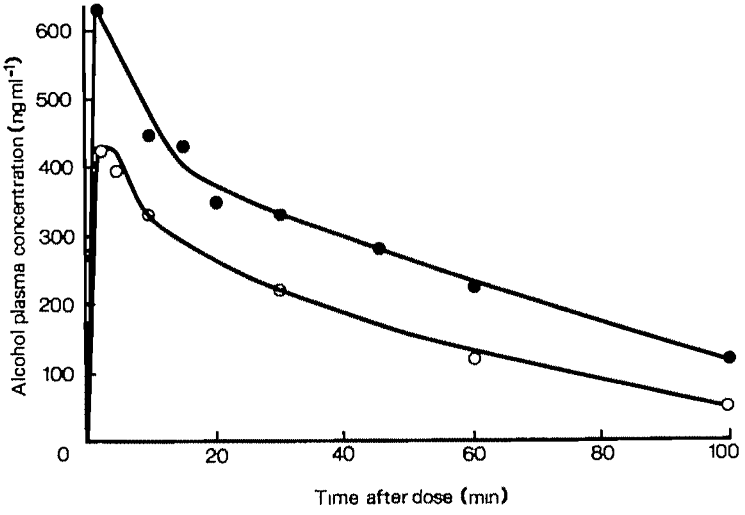

FIG. 5. Plasma concentrations of monoquaternary alcohol in a selected normal patient (○) and a renal failure patient (●) after a 0.3-mg kg^{-1} i.v. bolus dose of atracurium. The solid lines are computer fitted (see text).

TABLE V. *Pharmacokinetic parameters of atracurium derivatives (mean ± SD)*

	Normal ($n = 4$)	Renal failure ($n = 6$)	Variance test	t Test
Laudanosine				
Half-life (min)	197±38	234±81	ns	ns
Cl_{app} (ml min^{-1} kg^{-1})	10±1	8±5	ns	ns
Renal clearance (ml min^{-1} kg^{-1})	0.4±0.1 ($n = 3$)			
Monoquaternary alcohol				
Half-life (min)	26±4	39±29 ($n = 5$)	ns	ns
Cl_{app} (ml min^{-1} kg^{-1})	14±3	17±9 ($n = 5$)	$P < 0.05$	ns

TABLE VI. *Calculated steady state plasma concentrations (µg ml^{-1} after atracurium 0.6 mg kg^{-1} h^{-1}) (mean ± SD)*

	Normal	Renal failure	Variance test	t Test
Laudanosine	1.0±0.1 ($n = 4$)	1.6±0.8 ($n = 6$)	$P < 0.01$	ns
Range	0.96–1.1	0.54–2.33		
Monoquaternary alcohol	0.72±0.14 ($n = 4$)	0.72±0.33 ($n = 5$)	ns	ns
Range	0.56–0.83	0.33–1.15		

TABLE VII. *Urinary recovery of atracurium and laudanosine in normal patients after a bolus i.v. dose of atracurium 0.3 mg kg^{-1}*

	Patient No. 1	2	3	Mean ± SD
Atracurium (%)	6.3	2.4	10.4	6±4
Laudanosine (%)	3.7	3.1	3.8	3.5±0.4
Minimum renal clearance of atracurium (ml min^{-1} kg^{-1})	0.7	0.1	0.3	0.4±0.3

laudanosine in the three normal patients ranged from 2 to 10% of the dose administered for atracurium, and from 3 to 4% (by weight) for laudanosine (table VII). The minimal true renal clearance of atracurium was 0.4±0.3 ml min^{-1} kg^{-1}.

TABLE VIII. *Pharmacodynamic recovery times (min) for atracurium 0.3–0.4 mg kg^{-1}*

	T_{25-75} Normal	T_{25-75} Renal failure	T_{0-25} Normal	T_{0-25} Renal failure
	12	16	22	20
	10	14	32	31
	9	18	32	26
	10	20	33	30
Mean ($n = 4$)	10.3	17.0	30	27
SD	1.3	2.6	5	5
Variance test	ns		ns	
t Test	$P < 0.01$		ns	

Arterial pressure and heart rate were not significantly altered by anaesthesia or surgery. However, recovery times from neuromuscular blockade (T_{25-75}) were significantly prolonged in the group in chronic renal failure when compared with the normal group, whereas durations of blockade (T_{0-25}), were decreased—although not significantly (table VIII).

DISCUSSION

Pharmacokinetics and pharmacodynamics of atracurium

The authors have used the previously-reported pharmacokinetic parameters for atracurium obtained following the administration of 0.3 mg kg^{-1} to normal patients as controls to compare with those obtained in a group of patients in renal failure given a similar dose. This is considered justifiable since, in both studies, the clinical work was carried out at the same hospital by the same principal investigator, and the analyses of concentrations (although by a different HPLC method) were carried out in the same laboratory. Atracurium concentrations *were* measured in the small ($n = 4$) normal group, and although the concentrations were as expected for the doses given, as a result of the small dose and the sampling times which were designed to determine the derivative profiles, only six samples from each normal patient gave measurable concentrations of atracurium. These were not sufficient to define the pharmacokinetic parameters with any meaningful precision. In contrast, there was a minimum of eight samples for each patient in the renal failure group, which was sufficient to estimate acceptably the pharmacokinetic parameters.

Given the above justification, this study has demonstrated that the pharmacokinetic profile of atracurium is not affected significantly by the absence of renal function. These results agree with those in a recent similar study (Fahey et al., 1984), in which atracurium was given as a 0.5-mg kg^{-1} bolus. The relatively short elimination half-life ($T_{\frac{1}{2}}^{\beta} = 20$ min) has also been shown to be unaffected by hepatic failure in adults (Ward and Neill, 1983) and in children (Cook et al., 1984). These findings emphasize the clinical importance of the pH and temperature-dependent removal of the atracurium molecule from the body independently of the usual elimination pathways—the liver and the kidney.

The measurement of atracurium in the urine of the normal patients, amounting to 2–10% of the dose, demonstrates that atracurium is partly cleared by the kidney. Over the time of the study (500 min) atracurium in the bladder would be expected to undergo appreciable Hofmann degradation unless the pH was sufficiently acidic (less than 6) to inhibit substantially this breakdown. The urinary clearance reported here must be an underestimate as a result of the loss of an indeterminate amount of atracurium by the above argument, but its presence at all must increase the elimination half-life of atracurium in the case of renal failure.

Consideration of pharmacokinetic reports (Ward and Neill, 1983; Cook et al., 1984; Fahey et al., 1984) of atracurium given to patients with some degree of renal or hepatic impairment, shows a slight, but not statistically significant, increase in terminal half-life relative to normal patients, thus confirming the presence of (necessarily minor) organ-based routes of elimination of atracurium. A consequence of this slight increase in terminal half-life, for a neuromuscular blocking agent with the pharmacodynamic recovery phase occurring during the elimination rather than the distribution phase (where distribution also includes the kinetics of drug movement through the receptor region), is that, irrespective of changes in volumes of distribution, the time for recovery from blockade (T_{25-75}) must increase. The appendix shows that, for example, a 4% increase in $T_{\frac{1}{2}}^{\beta}$ would give rise to a 4% increase in recovery time. The increase in $T_{\frac{1}{2}}^{\beta}$ found in this paper (19.3 min in normal patients, to 20.1 min in renal failure—a 4% increase) would, therefore, be expected to increase the recovery time for the single twitch from 14.4 to 15.0 min. The direction but not the magnitude of the increase measured (10.3 to 17.0), is in accordance with the theory. This is in agreement with previously reported non-significant changes in $T_{\frac{1}{2}}^{\beta}$ (20.6 to 23.7 min) and T_{25-75} (10.5 to 13.1 min) when comparing normal patients with those in renal failure (Fahey et al., 1984), where the theory would predict twitch recovery changes from 15.4 to 17.7 min for the above increase in $T_{\frac{1}{2}}^{\beta}$. Duration of neuromuscular blockade (in this paper, from time of injection to 25% recovery of single twitch), is not such a simple function of the elimination half-life, but depends upon the dose and distribution volumes and kinetics in a complex relationship; prediction cannot be made in the simple way that applies to all symmetrical recoveries.

Pharmacokinetics of metabolites

Atracurium was designed to undergo rapid chemical inactivation by "Hofmann elimination", fission occurring at the quaternary nitrogen, to give laudanosine and monoquaternary acrylate, and ester hydrolysis to give monoquaternary acid and alcohol (Stenlake et al., 1983) (fig. 1). Recently, concern was expressed as to the properties of these metabolites (Agoston and Langrehr, 1984). In the original pharmacological studies in animals it was shown that untoward side effects were minimal at doses of 4 mg kg^{-1} of each metabolite when given to anaesthetized cats (Chapple and Clarke, 1983). In the clinical environment the present study has shown that there are two significant metabolites in renal failure: the monoquaternary alcohol, peak concentration 0.43 μg ml^{-1} with an elimination half-life of 39 min and laudanosine, peak concentration 0.27 μg ml^{-1}, with an elimination half-life of 234 min.

Laudanosine, with the longer half-life, would appear to be the metabolite causing most concern. A tertiary amine, it is a glycine antagonist and strychnine-like effects have been described with this compound (Pong and Graham, 1976). In experimental animals doses of 21 mg kg^{-1} (Babel, 1899) and 13–22 mg kg^{-1} (Hennis et al., 1984) produced convulsions, with doses of 9–10 mg kg^{-1} (Mercier and Mercier, 1955) producing epileptic patterns on the EEG. Plasma concentrations producing these effects were not provided, although laudanosine 1 mg kg^{-1} gave peak plasma concentrations of between 0.5 and 1.0 μg ml^{-1} (Hennis et al., 1984). Recent work in anaesthetized dogs (Chapple et al., 1987) has shown that convulsions do not occur at plasma laudanosine concentrations of less than 17 μg ml^{-1}. To obtain this value in man as an early peak concentration would require bolus doses in excess of 15 mg kg^{-1}, which would be an intubating dose about 20 times that recommended.

The kinetic profile of laudanosine is markedly different from that of atracurium, with a final elimination half-life more than 10 times that of atracurium. This will mean the plasma laudanosine concentrations will increase during multiple "top ups" or during continuous infusions of atracurium. During a continuous infusion of atracurium to maintain a plasma concentration of 2 µg ml^{-1} (> 95% neuromuscular blockade) a continuous pseudoinfusion of laudanosine will occur with increasing plasma concentrations until a steady state is achieved. This plateau concentration of laudanosine might be expected to be around 1 µg ml^{-1} in normal patients and 1.6 µg ml^{-1} in patients with renal failure, after 16–20 h of an infusion of atracurium (5 to 6 laudanosine elimination half lives (table VI)).

In order to predict the behaviour of laudanosine and monoquaternary alcohol in clinical situations outside those covered in the present study (for example, for infusion during routine surgery or even longer), an objective simplified model system was used (fig. 2). It was assumed that the formation of each metabolite took place in the atracurium central compartment (although the peripheral compartment must supply it also), the metabolite was then distributed between a central and peripheral compartment, and it was then eliminated finally from its central compartment. The assumption that the atracurium kinetics can be calculated, rather than actual measurements used, makes no appreciable difference to the fitted kinetic profile of the metabolites and, consequently, neither to the estimation of the terminal half-life nor the apparent clearance (calculated by dose of atracurium divided by area under the metabolite plasma concentration curve from zero time to infinity). The use of a model allows a small objective constraint to be placed on the plasma data, so that the data can be used in more than just a purely descriptive way.

In a recent study (Fahey et al., 1985) on the plasma profile of laudanosine in normal and renal failure patients, the authors have used such a purely descriptive method. Their results, after scaling down from the higher atracurium bolus dose used (0.5 mg kg^{-1}), are very similar, in the mean plasma profiles observed, to those in the present study (compare figure 3 in the present study with figure 1 in the reference). Unfortunately, their descriptive method did not provide estimates of half-lives or apparent clearances.

The model approach illustrates for laudanosine with selected actual results (fig. 4), the early (~ 2 min) peak concentration of laudanosine, which appears to be affected little by renal failure, and is, therefore, probably a result of the direct Hofmann degradation of atracurium itself from the plasma compartment.

The early peak declines rapidly, probably as a result of the distribution of laudanosine into its peripheral compartment. The plateau (or sometimes maximum), predicted from the model and the final long decay, are caused by a combination of redistribution from the peripheral compartment, formation of laudanosine from other breakdown products of atracurium and, of course, the removal of laudanosine by metabolism or direct organ clearance.

The measurement of the urinary clearance of laudanosine (amounting to only 3% by weight of the original atracurium), is probably an overestimate, as the laudanosine directly excreted is augmented by Hofmann breakdown in the bladder of any atracurium derivatives still containing the unchanged quaternary group (fig. 1). However, the elimination half-life of laudanosine must increase in renal failure, although this increase does not reach statistical significance, and would be expected to produce only a slightly higher steady state laudanosine plasma concentration during a prolonged infusion of atracurium.

It is probable that the major removal of laudanosine is metabolic and, therefore, it would be expected that the terminal half-life of laudanosine might increase significantly if metabolic pathways were constrained, for example in the case of hepatic disease (Vine et al., 1986).

APPENDIX

RECOVERY OF NEUROMUSCULAR BLOCKADE FOR AN AGENT WITH RELEVANT KINETICS ON ELIMINATION PHASE

Using the nomenclature and model from the previously cited study (Weatherley, Williams and Neill, 1983; figure 4) (see also figure 2 of this paper), the concentrations of atracurium in the central (C_c) and effect (C_e) compartment at any time t are given by the equations:

$$C_c = Ae^{-\alpha t} + Be^{-\beta t} \tag{1}$$

$$C_e = k_{30}\left(\frac{A.\text{dose}}{(k_{30}-\alpha)}(e^{-\alpha t} - e^{-k_{30}t}) + \frac{B.\text{dose}}{(k_{30}-\beta)}(e^{-\beta t} - e^{-k_{30}t})\right) \tag{2}$$

where k_{30} is the removal rate constant from the receptor compartment, α and β are the atracurium distribution and elimination rate constants, respectively, A and B are the normalized (to μg ml^{-1} mg^{-1} kg^{-1}) atracurium plasma concentration multipliers, and the dose is expressed in mg kg^{-1}. Provided $k_{30} > \beta$, and the dose is large enough that the recovery phase from neuromuscular block occurs at sufficiently long time, then:

$$C_e \cong \frac{B.k_{30}.\text{dose}}{(k_{30}-\beta)}.e^{-\beta t} = Pe^{-\beta t} \tag{3}$$

where

$$P = \frac{B.k_{30}.\text{dose}}{(k_{30}-\beta)} \tag{4}$$

These conditions are fulfilled for atracurium ($\beta = 0.035$, $k_{30} = 0.1$ for twitch, $k_{30} = 0.208$ for tetanus response), provided the dose is no smaller than 0.3 mg kg^{-1}. (If $k_{30} < \beta$, then the recovery would depend on the half-life of removal of blocking agent from the receptor region, rather than removal from the plasma compartment.) The equation for response (R) is:

$$R = \frac{R_{\max}}{1+\left(\frac{C_e}{C_{50}}\right)^s} \tag{5}$$

where $R_{\max}$ is the maximum twitch achievable (100% before dosing), C_{50} the concentration in the receptor compartment to achieve 50% maximum block, and s is the Hill coefficient relating to the steepness of the concentration–response curve.

For the particular case of R_{25} (25% of full response):

$$R_{25} = \frac{R_{\max}}{1+\left(\frac{C_{25}}{C_{50}}\right)^s} = \frac{R_{\max}}{4} \tag{6}$$

By simple manipulation:

$$\left(\frac{C_{25}}{C_{50}}\right)^s = 3 \tag{7}$$

Taking logarithms to base e:

$$\ln(C_{25}) - \ln(C_{50}) = \frac{1}{s}.\ln(3) \tag{8}$$

Similarly, for R_{75} (75% of full response):

$$\ln(C_{75}) - \ln(C_{50}) = \frac{1}{s}.\ln(\tfrac{1}{3}) \tag{9}$$

Now equation (3) after taking logarithms gives:

$$\ln(C_{25}) = \ln(P) - \beta t_{25} \tag{10}$$

similarly

$$\ln(C_{75}) = \ln(P) - \beta t_{75} \tag{11}$$

where t_{25} and t_{75} are the times to 25% and 75% recovery, respectively.

Subtraction of (11) from (10) gives

$$\ln(C_{25}) - \ln(C_{75}) = \beta(t_{75} - t_{25}) \tag{12}$$

and subtraction of (9) from (8) gives:

$$\ln(C_{25}) - \ln(C_{75}) = \frac{1}{s}.\ln(3) - \frac{1}{s}.\ln(\tfrac{1}{3}) \tag{13}$$

Equating the right-hand sides of (12) and (13) gives

$$\text{Recovery time, } t_{75} - t_{25} = \frac{2.\ln(3)}{s\beta} = \frac{\ln(9).T_{\frac{1}{2}}^{\beta}}{s.\ln(2)} \tag{14}$$

where $T_{\frac{1}{2}}^{\beta}$ is the elimination half-life.

Hence, the recovery time is directly proportional to the elimination half-life and inversely proportional to the Hill coefficient. For single twitch, $s = 4.25$, $\beta = 0.035$ gives a recovery time of 14.8 min, and even if renal failure changes the volumes of distribution or other disposition constants (A, B, α and β all change), only the change in β has an effect upon recovery time from blockade provided the Hill coefficient is not altered.

Recovery of tetanic response also obeys equation (14), and the Hill coefficient of $s = 2.98$ with the same β gives a predicted recovery time of 21.1 min.

Any other symmetrical recovery interval can be treated in a similar way. For example the time from 5% to 95% recovery would be given by

$$t_{95} - t_5 = \frac{2.\ln(19)}{s\beta} \tag{15}$$

provided that the dose is sufficiently large for the previously described conditions to remain valid.

The equation for duration of blockade (for example time to 25% recovery, t_{25}), is obtained by re-arranging (10) to give

$$t_{25} = \frac{\ln(P) - \ln(C_{25})}{\beta} \tag{16}$$

and substituting for $\ln(P)$ from (4) and $\ln(C_{25})$ from (8) leads to

$$t_{25} = \frac{\ln(\text{dose})}{\beta} + \frac{\ln\left(\frac{B.k_{30}}{k_{30}-\beta}\right) - \ln(C_{50}) - \frac{1}{s}.\ln(3)}{\beta} \tag{17}$$

The second term on the right is a complex function of the pharmacokinetic and pharmacodynamic variables and, therefore, the effect of renal failure on the duration of blockade is difficult to predict. If a single subject, however, were studied at different doses, this term would be constant, and the *change* in t_{25} would be expected to be proportional to the logarithm of the dose ratio and inversely proportional to β, but independent of the Hill coefficient.

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EFFECTS OF ALFENTANIL ON THE PRESSOR AND CATECHOLAMINE RESPONSES TO TRACHEAL INTUBATION

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SUMMARY

The effects of alfentanil (given during induction of anaesthesia) on the haemodynamic and catecholamine responses to tracheal intubation were studied in 44 adult patients who received alfentanil 10 μg kg^{-1} or 40 μg kg^{-1}, or saline placebo. Alfentanil 10 μg kg^{-1} and 40 μg kg^{-1} prevented any increase in heart rate and arterial pressure after tracheal intubation. Alfentanil 40 μg kg^{-1} produced profound hypotension and bradycardia. The use of alfentanil in both doses was associated with a decrease in plasma adrenaline concentrations after tracheal intubation.

Laryngoscopy and intubation are associated with increases in arterial pressure, heart rate and plasma catecholamine concentrations (Derbyshire et al., 1983)—haemodynamic responses which may be accompanied by myocardial ischaemia and increased myocardial oxygen demand (Prys-Roberts et al., 1971). The pressor response can be blocked by high doses of opioids (Lunn et al., 1979) given during the induction of anaesthesia, and attenuated by low doses of fentanyl (Martin et al., 1982), volatile anaesthetics (Bedford and Marshall, 1984), local anaesthetics (Stoelting, 1978; Dohi et al., 1982), α-adrenoceptor blockers (Curran, Crowley and O'Sullivan, 1980), β-adrenoceptor blockers (Prys-Roberts et al., 1971) and drugs with vasodilating properties (Stoelting, 1979). The catecholamine response is modified by the use of large doses of opioids (Delange et al., 1983), and a number of neuromuscular blocking drugs (Cummings, Russell and Frewin, 1983). Although the most reliable method for preventing the catecholamine and haemodynamic responses appears to be the use, during induction, of large doses of opioids, any technique using fentanyl in excess of 10 μg kg^{-1} at induction may lead to postoperative ventilatory depression.

The introduction of the ultra short-acting opioid, alfentanil, permitted the use of a high-dose opioid induction technique without the concomitant risk of postoperative ventilatory depression. Black, Kay and Healy (1984) showed that alfentanil 15 μg kg^{-1} i.v. modified the haemodynamic changes and that 30 μg kg^{-1} abolished the pressor response in healthy patients undergoing elective surgery.

In the present study, alfentanil 10 μg kg^{-1} and 40 μg kg^{-1} were administered i.v. as part of the anaesthetic induction sequence, and the effects on the sympathoadrenal response to tracheal intubation were studied. These doses were chosen to equate with low (2–3 μg kg^{-1}), or medium (10 μg kg^{-1}) dose fentanyl in the ratio alfentanil: fentanyl of 4 : 1 (Rucquoi and Camie, 1983).

PATIENTS AND METHODS

Forty-four patients were studied, during major vascular, head and neck or thoracoabdominal surgery where direct arterial monitoring was planned as part of the anaesthetic technique. District Ethical Committee approval was obtained and each patient gave informed consent.

Patients were allocated randomly to receive i.v. over 30 s (as part of the anaesthetic induction sequence) a 10-ml bolus containing either alfen-

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tanil 10 µg kg^{-1} (A10), alfentanil 40 µg kg^{-1}, (A40) or saline placebo (S).

Each patient was premedicated with diazepam 10 mg orally, given 90 min before operation. In the anaesthetic room, arterial and i.v. cannulae were inserted under local anaesthesia. Direct arterial pressure monitoring was commenced, and the ECG (lead II) was displayed. After a 10-min stabilization period arterial blood was drawn for catecholamine analysis, and arterial pressure and heart rate were recorded simultaneously by an independent observer.

Induction of anaesthesia was achieved with sufficient thiopentone (3–5 mg kg^{-1}) to obtund the eyelash reflex, given i.v. over 1 min and was immediately followed by vecuronium 0.1 mg kg^{-1}. After 30 s the study drug was administered. Ventilation was assisted, then controlled, using an anaesthetic face mask and a coaxial Mapleson D breathing system with a fresh gas flow of 33% oxygen in nitrous oxide 70 ml kg^{-1} to maintain an end-expired carbon dioxide concentration of approximately 5% (Gould capnograph). One minute after the administration of the study drug, heart rate and arterial pressure were recorded and arterial blood drawn for catecholamine analysis. Ninety seconds after the administration of the study drug the patient's trachea was intubated with the aid of a standard Macintosh laryngoscope blade, and anaesthesia was continued with nitrous oxide in oxygen and positive pressure ventilation—which was adjusted, if necessary, so as to maintain normocapnia.

Further samples and measurements were taken at 1, 3 and 5 min after intubation. Throughout the study period, both observer and anaesthetist were unaware of the nature of the study drug. The anaesthetist was permitted to use increments of thiopentone to treat clinically inadequate anaesthesia or to increase the rate of the i.v. infusion to correct unacceptable degrees of hypotension. At the end of the study period, anaesthesia and surgery continued using additional anaesthetic agents as appropriate.

Arterial blood for measurement of plasma concentrations of adrenaline and noradrenaline was collected in lithium heparin tubes and centrifuged within 1 h at 0 °C. Plasma was separated and stored at −70 °C before assay was peformed by HPLC using a method described previously (Derbyshire et al., 1983).

Statistical analysis was by a two-way analysis of variance and Student's *t* test (paired within groups and unpaired between groups). A *P* value of less than 0.05 was deemed significant.

TABLE I. *Demographic data (mean ± SEM)*

	Control	A10	A40
n	15	14	15
Age (yr)	66.1 (2.8)	67.0 (2.2)	65.7 (2.3)
M:F	12.3	10:4	11:4
Wt (kg)	70.0 (3.1)	63.0 (4.2)	67.0 (2.1)
MAP (mm Hg)	100.7 (4.1)	108.5 (4.7)	103.5 (4.8)
HR (beat min^{-1})	84.2 (3.9)	78.5 (4.5)	75.7 (3.6)

RESULTS

The three groups were comparable in respect of age, weight and gender (table I). There were no significant differences between the three groups in the baseline (preinduction) values for mean arterial pressure (MAP) or heart rate (HR). Twenty-two patients were receiving concurrent

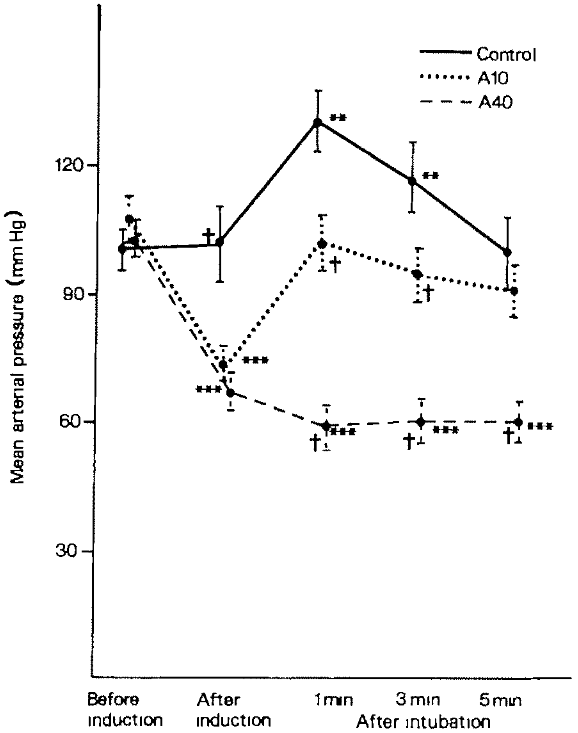

FIG. 1. Mean arterial pressure. $^{**}P < 0.01$ within group in comparison with value before induction; $^{***}P < 0.001$ within groups in comparison with value before induction; $^{\dagger}P < 0.05$ between group comparison.

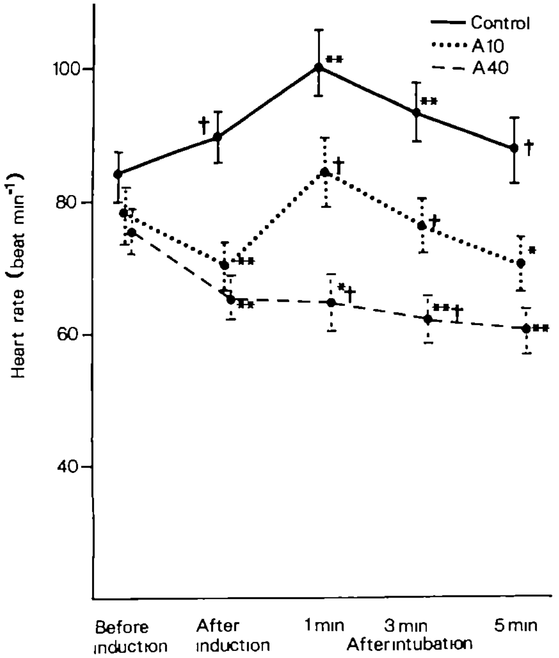

FIG. 2. Heart rate. *$P < 0.05$ within group in comparison with value before induction; **$P < 0.01$ within group in comparison with value before induction; †$P < 0.05$ between group comparison.

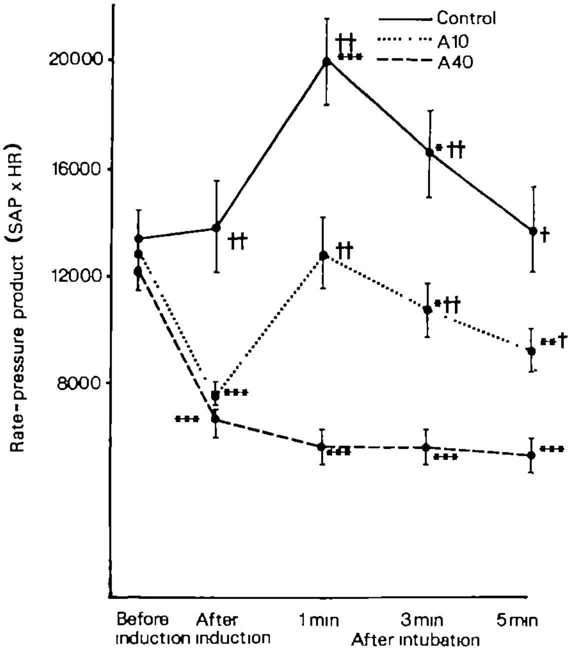

FIG. 3. Rate–pressure product. *$P < 0.05$ within group in comparison with value before induction; **$P < 0.01$ within group in comparison with value before induction; ***$P < 0.001$ within group in comparison with value before induction; †$P < 0.05$ between group comparison; ‡$P < 0.001$ between group comparison.

medication with β-adrenoceptor blockers or other antihypertensive agents; they were evenly distributed between the three groups.

The results for mean arterial pressure (MAP) are shown in figure 1. In the control group (S), there was a significant increase above preinduction values at 1 and 3 min after intubation ($P < 0.01$). In both treatment groups, MAP decreased significantly on induction ($P < 0.001$). After intubation in the A10 group, MAP returned to preinduction values, whereas in the A40 group MAP decreased further to 59 mm Hg (±4.5) ($P < 0.05$). This value was significantly lower than that for both control and A10 groups ($P < 0.001$). Eleven patients in the A40 group received more than 750 ml of fluids i.v. to maintain mean arterial pressure at 60 mm Hg.

Heart rate increased in the control group 1 min after intubation ($P < 0.01$) (fig. 2). In the A10 group there was a decrease in heart rate after the induction of anaesthesia ($P < 0.01$), and at 5 min after intubation ($P < 0.05$). Heart rates in the A40 group were significantly lower than the preinduction heart rate in this group after induction and intubation ($P < 0.05$).

Heart rates in the two treatment groups were significantly slower than those of patients in the control group at all times after induction, and differed between the two alfentanil groups at 1 and 3 min after intubation. Five patients in the A40 group received atropine i.v. in response to bradycardia associated with hypotension.

Figure 3 shows the values for rate–pressure product (RPP) in the three groups. RPP was increased in the control group at 1 and 3 min after intubation. In the treatment groups there were significant decreases after induction ($P < 0.001$). In the A10 group RPP was significantly less than that before induction at 3 and 5 min. In the A40 group there was a further decline in RPP after intubation and the RPP remained lower than the preinduction value throughout the study period ($P < 0.001$). Following the induction of anaesthesia, the two treatment groups demonstrated a significantly lower RPP than that of the control group and the RPP differed significantly between the three groups after intubation.

Plasma noradrenaline concentrations were determined in blood samples from 17 patients (fig. 4).

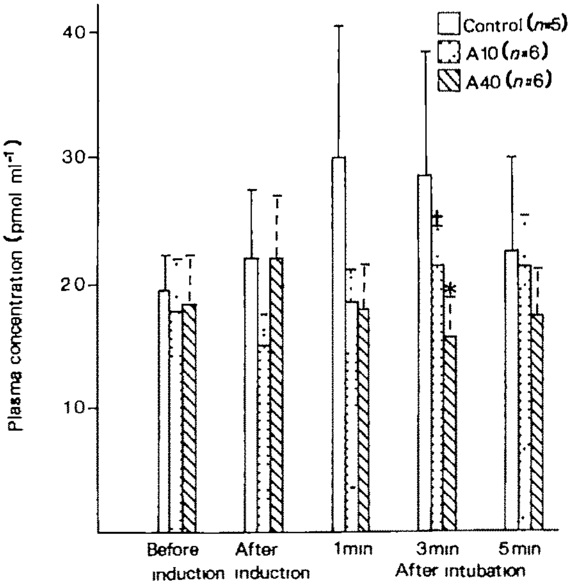

FIG. 4. Plasma noradrenaline concentrations. $^{*}P < 0.05$ within group comparison with value after induction; $^{\dagger}P < 0.01$ within group in comparison with values after induction.

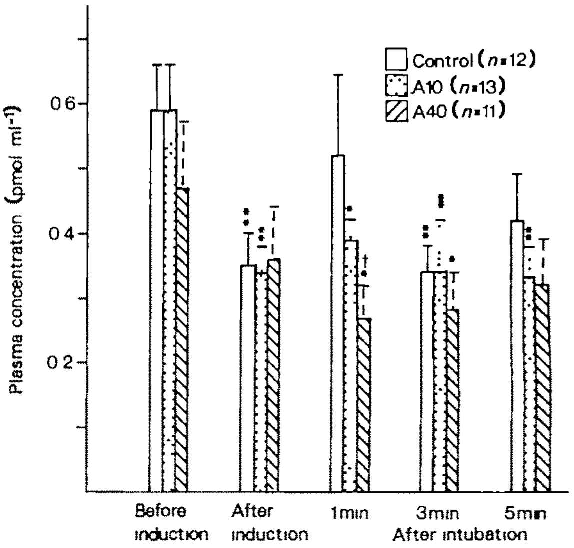

FIG. 5. Plasma adrenaline concentrations. $^{*}P < 0.05$ within group in comparison with value before induction; $^{**}P < 0.01$ within group in comparison with value before induction; $^{\dagger}P < 0.05$ in comparison with the A10 group.

There was a 50% increase (from preinduction) in noradrenaline concentration in the control group 1 min after intubation, but this was not statistically significant. In the A10 group, there was an increase in plasma noradrenaline between the sample taken after induction and the one taken 3 min after intubation ($P < 0.01$) while in the A40 group, noradrenaline concentration declined at 3 min in comparison with that after induction ($P < 0.05$). There were no significant differences between the three groups.

Figure 5 depicts the changes in the plasma adrenaline concentrations determined in samples from 36 patients. In both treatment groups plasma adrenaline concentration decreased at 1 and 3 min after intubation ($P < 0.05$). The value at 1 min was significantly lower in the A40 group than the A10 group ($P < 0.05$).

Six patients in the control group and one patient in the A10 group each required one increment of thiopentone. Four patients in the control group and one patient in the A10 group exhibited ECG arrhythmias, but none required treatment. No patients displayed ECG signs of ischaemia.

There was no morbidity attributable to anaesthesia and no patient in the A40 group required naloxone at the end of surgery despite liberal use of other opioid drugs during surgery.

DISCUSSION

This study has confirmed previous work that intubation of the trachea following thiopentone and a neuromuscular blocking drug is associated with significant increases in heart rate and mean arterial pressure (Derbyshire et al., 1983). Alfentanil in doses of 10 µg kg^{-1} and 40 µg kg^{-1} prevented the increases in mean arterial pressure and heart rate, in contrast to results from other authors where alfentanil 15 µg kg^{-1} failed to obtund the tachycardia (Black, Kay and Healy, 1984). In the present study, this may result from the use of a non-depolarizing myoneural blocking drug with stable cardiovascular properties (vecuronium) rather than the shorter acting suxamethonium which may have led to an increase in heart rate as spontaneous ventilation recommenced.

The decreases in mean arterial pressure demonstrated in both treatment groups after the induction of anaesthesia were maintained after intubation in the group who received the larger dose of alfentanil, and were unacceptably low to the "blind" anaesthetist. Much of the previously published work demonstrating the cardiostability of alfentanil has used alfentanil or etomidate as the induction agent, with oxygen-enriched air, ventilation and pancuronium as the myoneural blocking drug, and this may account for the apparent discrepancy between that and the present results obtained during the use of the non-vagolytic drug, vecuronium.

A decrease in mean arterial pressure has been reported previously after alfentanil 150 µg kg^{-1} (Moldendenhaur et al., 1983), 120 µg kg^{-1} (Rucquoi and Camie, 1983), 70 µg kg^{-1} (Spiss et al., 1984) and 30 µg kg^{-1} (Black, Kay and Healy, 1984). The magnitude of the decrease in MAP (40%) observed in the present study has not been reported previously and may reflect our use of ASA grade III patients. The resistance of the hypotension to treatment with i.v. fluids or atropine, or both, would tend to support the work of Moldenhaur and colleagues (1983), who suggested that alfentanil produced a degree of direct myocardial depression.

Despite evidence in animals that cerebral blood flow is preserved in the presence of alfentanil-induced hypotension (McPherson et al., 1985) and the lack of reports of anaesthetic morbidity, the results of our study suggest that it may be inappropriate to use a high dose technique in patients with potential atheromatous cerebrovascular disease.

In contrast to the high-dose group, patients receiving alfentanil 10 µg kg^{-1} demonstrated a restoration of mean arterial pressure after intubation to values similar to those obtained before induction. In addition, the increase in rate-pressure product seen in the control group after intubation was obtunded by the smaller dose of alfentanil (fig. 3). Thus alfentanil 10 µg kg^{-1} has been shown (in this study) to exert a stabilizing effect upon these indices of the haemodynamic response to tracheal intubation.

Catecholamine responses to intubation have not previously been documented in association with the use of vecuronium, but various studies have shown differing plasma concentrations of noradrenaline with suxamethonium (Russell et al., 1981), pancuronium (Derbyshire et al., 1983), alcuronium (Cummings, Russell and Frewin, 1983) and tubocurarine (Cummings et al., 1983). The failure in this study to demonstrate any significant change in plasma noradrenaline concentrations may well result from the fact that, for technical reasons, samples were obtained from only a relatively small number of patients. If vecuronium is associated with smaller changes in noradrenaline concentration in contrast to those observed when pancuronium is used, it may be necessary to study catecholamine concentrations in central venous blood samples, since these could be expected to exhibit a greater change than arterial samples—as it is known that noradrenaline is selectively taken up by the lungs (Ginn and Vane, 1968).

The data relating to plasma adrenaline concentrations agree with the suggestion of Russell and colleagues (1981) that the induction of anaesthesia causes a significant decrease in adrenaline concentration. In the present study the change was more marked in the high-dose alfentanil group in comparison with the low-dose group immediately after intubation. This decrease in adrenaline concentration was sustained for up to 3 min after intubation in both treatment groups, and up to 5 min in the low-dose alfentanil group, a pattern which was not mirrored by the haemodynamic data. However, immediately after intubation, concentrations in the control group returned to preinduction values, in contrast to those for the two treatment groups. This contrasts with earlier work from this Department which demonstrated an increase in plasma noradrenaline concentration with suxamethonium but not with pancuronium, again stressing the variation in catecholamine concentrations seen with various neuromuscular blockers (Derbyshire et al., 1983).

In conclusion, this study has shown that alfentanil 40 µg kg^{-1} in combination with an anaesthetic technique comprising thiopentone, nitrous oxide and vecuronium, prevented the haemodynamic and catecholamine responses to intubation. However, this dose produced profound hypotension and bradycardia which were resistant to volume replacement and atropine. Alfentanil 40 µg kg^{-1} cannot, therefore, be recommended for use in patients in whom a cardiostable induction is desirable. However, alfentanil 10 µg kg produced a more stable cardiovascular system and we would recommend this dose since, in the present investigation, it prevented haemodynamic variables from increasing above their baseline values immediately after intubation, whilst both doses were associated with a reduction in plasma adrenaline concentrations. It should be emphasized, however, that such recommendations relate to patients who have not received atropine but to whom a non-vagolytic neuromuscular blocking drug has been administered.

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FENTANYL AND THE β-ENDORPHIN, ACTH AND GLUCOREGULATORY HORMONAL RESPONSE TO SURGERY

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SUMMARY

The effect of the supplementation of nitrous oxide–oxygen anaesthesia with either fentanyl 15 μg kg⁻¹ or 0.5% halothane on the β-endorphin, ACTH, glucoregulatory hormonal and metabolic response to pelvic surgery was investigated. Fentanyl inhibited the increases in circulating β-endorphin, ACTH, growth hormone, cortisol and glucose concentrations found in the patients receiving halothane. Changes in circulating β-endorphin concentrations during surgery probably reflect alterations in pituitary secretion and appear to have no major metabolic effects. The suppression of pituitary secretion persisted for at least 4 h after the start of surgery

The concomitant secretion of the peptides β-endorphin and adrenocorticotrophic hormone (ACTH) from the pituitary in response to acute stress was described initially in the rat by Guillemin and colleagues (1977). Since then an increase in circulating β-endorphin concentration has been described in a variety of clinical conditions such as labour (Akil et al., 1979; Fletcher, Thomas and Hill, 1980; Goland et al., 1981), hypoxia (Yanagida and Corssen, 1981), haemorrhagic shock (Shatney et al., 1985) and surgery (Dubois et al., 1981; McIntosh et al., 1985). However, the effects of different anaesthetic techniques on the changes in plasma β-endorphin concentration associated with surgery have received little attention. Dubois and co-workers (1982) found that fentanyl 10–20 μg kg^{-1} attenuated the β-endorphin response to laparotomy during the surgical procedure compared with patients who received enflurane. On the contrary, during cardiac surgery, Cork, Hameroff and Weiss (1985) observed that fentanyl 50–100 μg kg^{-1} and halothane had similar effects on plasma β-endorphin values. In both these studies, however, the changes in β-endorphin concentration were described in isolation, with few data on the associated changes in the other pituitary hormones commonly used to assess the endocrine response to surgery.

The purpose of the present study was to investigate the effects of fentanyl on the β-endorphin, ACTH and glucoregulatory hormonal response to surgery, together with the associated changes in the circulating metabolites.

PATIENTS AND METHODS

Fourteen healthy patients admitted for Fallopian tubal surgery were investigated. The patients were allocated randomly to receive supplementation of anaesthesia with either fentanyl 15 μg kg^{-1} or 0.5% halothane. The nature of the study was explained to the patients and consent obtained for the collection of central venous blood. The study was approved by the local Ethical Committee.

All patients were premedicated with diazepam 10 mg by mouth 2 h before surgery. On arrival in the anaesthetic room the duration of starvation was determined and a central venous catheter was inserted percutaneously from a vein in an antecubital fossa to permit blood sampling, and

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the administration of fluids. After the patient had rested for 10 min a control blood sample was collected, and the heart rate and arterial pressure were measured.

Anaesthesia was induced in all patients with thiopentone 4–5 mg kg^{-1}, the trachea was intubated with the aid of pancuronium 0.1 mg kg^{-1} and the lungs were ventilated with 70% nitrous oxide in oxygen. Patients in the fentanyl group received a bolus dose of fentanyl 15 μg kg^{-1} i.v. at the induction of anaesthesia, while patients in the control group received supplementation with 0.5% halothane throughout surgery. Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 4.5%. Sodium chloride solution 150 mmol litre^{-1} was administered i.v. at a rate of 6 ml kg^{-1} h^{-1} during and 2 ml kg^{-1} h^{-1} after operation. Measured blood loss did not exceed 200 ml.

Fifteen minutes after the induction of anaethesia another blood sample was collected and surgery commenced. Further samples were obtained 20 and 40 min and 1, 2, 4 and 6 h after the start of surgery. At the same time as the blood samples were collected, arterial pressure and heart rate were measured. Pain was assessed 1, 2 and 4 h after operation using a linear analogue scale from 0 to 10 (Bond and Pilowsky, 1966), and analgesia was provided with papaveretum 15 mg i.m. on demand.

On the 3rd day after operation the skinfold thicknesses of the patients were measured and the percentage of fat to body weight calculated (Durnin and Womersley, 1974).

All blood samples were analysed in duplicate for glucose, lactate and glycerol concentrations, and haematocrit, by methods described previously (Hall et al., 1980). Plasma β-endorphin, ACTH, cortisol, growth hormone (GH), insulin and glucagon values were determined in the preinduction sample and in samples collected 20 min, 1 h and 4 h after the commencement of surgery. Immunoreactive β-endorphin was measured by a sensitive and specific radioimmunoassay (Immunouclear Corporation, Stillwater, Minnesota) which showed no cross-reactivity with β-lipotrophin or ACTH. The minimal detectable concentration was 5 pmol litre^{-1} and the interassay coefficient of variation was 11.7% at 19.3 pmol litre^{-1}. Plasma ACTH was measured by a modification of the method of Rees and colleagues (1971), the interassay coefficient of variation was 10.9%. Cortisol (Seth and Brown, 1978), GH (W.H.O. reference preparation for human GH), insulin (Soeldner and Sloane, 1965) and glucagon (Bloom and Long, 1982) concentrations were measured by established radioimmunoassays. Intra- and interassay coefficients of variation were 6.5% and 9.8% for cortisol, 5.9% and 8.0% for GH, 5.6% and 8.9% for insulin and 6.6% and 7.8% for glucagon.

The results for the hormones, metabolites and physiological variables are presented as mean values (±SEM). Statistical evaluation was undertaken using two-way and one-way analyses of variance, as appropriate. The ACTH values were subjected to logarithmic transformation before analysis because of a skewed distribution. Pain scores are presented as medians with ranges and were evaluated using the Wilcoxon two-sample test for unpaired data.

RESULTS

Details of the patients studied are shown in table I. There was no difference between the groups with respect to age, body weight, body type, duration of preoperative starvation and duration of surgery.

Plasma β-endorphin and ACTH concentrations (fig. 1)

In the halothane group, β-endorphin values increased significantly from 12.5 pmol litre^{-1} before the induction of anaesthesia to 49.9 pmol litre^{-1} after 20 min of surgery ($P < 0.001$).

TABLE I. *Details of patients studied (mean ± SEM)*

	Halothane group ($n = 7$)	Fentanyl group ($n = 7$)
Age (yr)	29.5±1.7	29.1±1.6
Weight (kg)	56.5±2.2	49.4±2.7
Duration of starvation (h)	13.4±1.0	12.5±0 8
Body fat (%)	30.1±0.6	30.5±0.4
Duration of surgery (min)	101±10	108±4

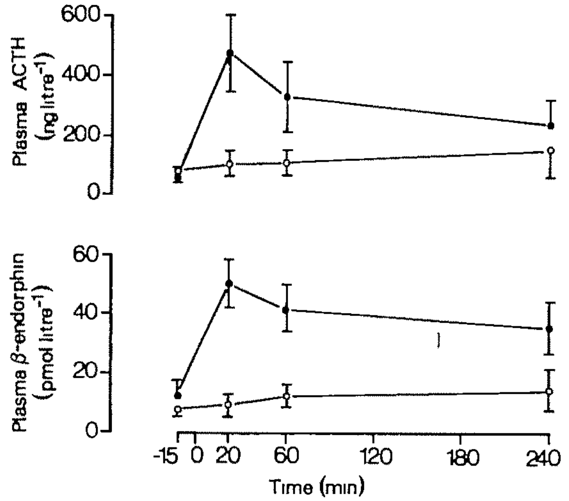

FIG. 1. Mean ($\pm$SEM) plasma β-endorphin (pmol litre^{-1}) and plasma ACTH (ng litre^{-1}) concentrations in patients receiving halothane (solid circles) or fentanyl (open circles). Surgery started at 0 min.

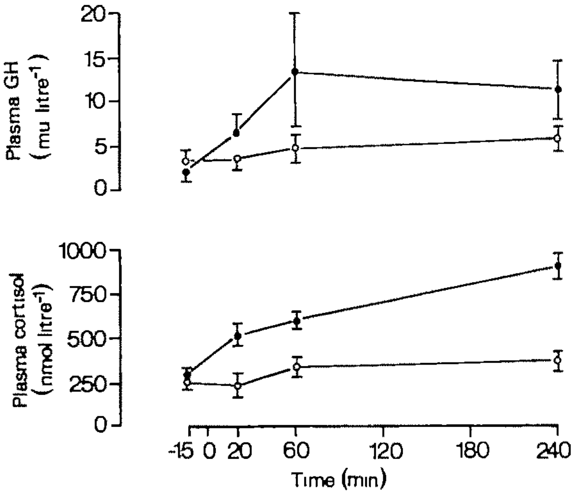

FIG. 2. Mean ($\pm$SEM) plasma cortisol (nmol litre^{-1}) and plasma GH (mu. litre^{-1}) concentrations in patients receiving halothane (solid circles) or fentanyl (open circles). Surgery started at 0 min.

This significant increase persisted until 4 h after the start of surgery (35.3 pmol litre^{-1}) ($P < 0.01$). In contrast, the fentanyl group showed no significant change from the pre-induction value either during or after surgery. There were significant differences between the groups after 20 min, 1 h and 4 h of surgery ($P < 0.01$, $P < 0.01$ and $P < 0.05$, respectively).

Changes in plasma ACTH concentration were similar in pattern to the changes noted in β-endorphin values. In the halothane patients there was a significant increase from 69 ng litre^{-1} before induction of anaesthesia to 475 ng litre^{-1} after only 20 min of surgery ($P < 0.001$) and values were still significantly increased 4 h after the start of surgery (237 ng litre^{-1}) ($P < 0.05$). The ACTH response to surgery was abolished in the fentanyl group and there was no significant increase from the preinduction value of 75 ng litre^{-1}. Significant differences between the groups were found after 20 min and 1 h of surgery ($P < 0.001$ and $P < 0.05$, respectively).

Plasma cortisol and GH concentrations (fig. 2)

In the halothane patients plasma cortisol concentration increased two-fold, from the preinduction value of 252 nmol litre^{-1} to 509 nmol litre^{-1} after 20 min of surgery ($P < 0.001$). Cortisol values increased throughout the study to 877 nmol litre^{-1} ($P < 0.001$) after 4 h surgery. In the fentanyl group, there was no significant change in cortisol concentration throughout the study. There were significant differences between the groups after 20 min, 1 h and 4 h ($P < 0.001$).

Plasma GH concentration increased in the halothane group from 1.6 mu. litre^{-1} to 13.4 mu. litre^{-1} after 1 h of surgery ($P < 0.05$) and was still increased after 4 h (10.9 mu. litre^{-1}) ($P < 0.05$). On the contrary, there was no significant increase from the preinduction value in the fentanyl patients. There was a significant difference between the groups after 1 h ($P < 0.05$).

Plasma insulin and glucagon concentrations (fig. 3)

Plasma insulin concentrations did not change significantly throughout the study in either group of patients.

Plasma glucagon values increased significantly in the fentanyl group from 15.0 pmol litre^{-1} before induction of anaesthesia to 24.6 and 26.4 pmol litre^{-1} after 1 h and 4 h of surgery ($P < 0.05$ and $P < 0.01$), respectively. In the halothane group no significant change in plasma glucagon was found. There was no significant difference between the groups.

Blood glucose concentration (fig. 4)

In the patients receiving halothane, blood glucose concentration increased from 3.94 to

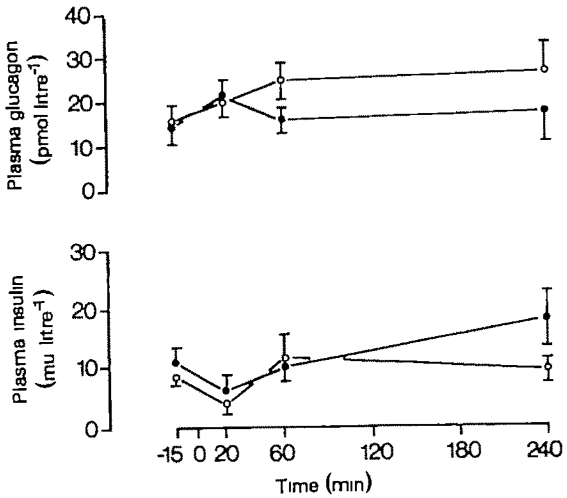

FIG. 3. Mean (±SEM) plasma insulin (mu. litre^{-1}) and plasma glucagon (pmol litre^{-1}) concentrations in patients receiving halothane (solid circles) or fentanyl (open circles). Surgery started at 0 min.

5.03 mmol litre^{-1} after 20 min of surgery ($P < 0.01$) and a significant increase persisted for the remainder of the study (5.21 mol litre^{-1} at 6 h) ($P < 0.05$). There was no significant change in blood glucose concentration in the fentanyl group. There were significant differences between the groups 40 min, 1 h and 2 h after the start of surgery ($P < 0.05$).

Blood lactate concentration (fig. 5)

Blood lactate values increased significantly during surgery in both groups of patients. After 1 h of surgery blood lactate concentrations had increased from 0.79 to 1.03 nmol litre^{-1} in the halothane group ($P < 0.01$) and from 0.66 to 1.07 mmol litre^{-1} in the fentanyl group ($P < 0.01$). Blood lactate concentrations decreased after the completion of surgery. There was no significant difference between the groups.

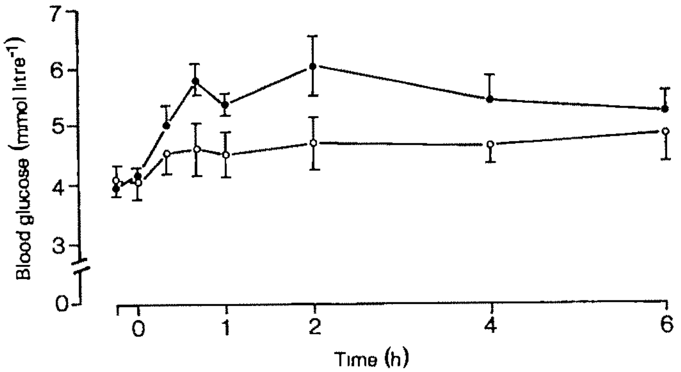

FIG. 4. Mean (±SEM) blood glucose (mmol litre^{-1}) concentrations in patients receiving halothane (solid circles) or fentanyl (open circles). Surgery started at 0 min.

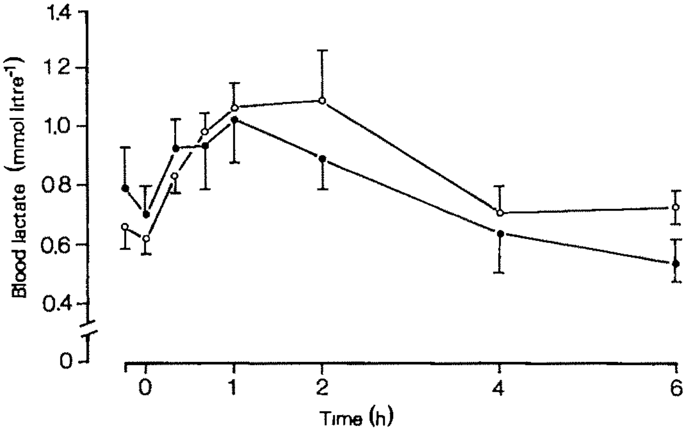

FIG. 5. Mean (±SEM) blood lactate (mmol litre^{-1}) concentrations in patients receiving halothane (solid circles) or fentanyl (open circles). Surgery started at 0 min.

Plasma glycerol concentration (fig. 6)

There were no significant changes in plasma glycerol concentration during the study in the halothane group. In the fentanyl patients the induction of anaesthesia was associated with a decrease in glycerol concentration from 140 to 80 μmol litre^{-1} ($P < 0.05$); thereafter, there were no significant changes from the preinduction value. There was no significant difference between the groups.

Arterial pressure and heart rate (fig. 7)

In the halothane group the induction of anaesthesia was associated with significant increases in mean arterial pressure ($P < 0.05$) and heart rate ($P < 0.01$). In those patients who received fentanyl, however, there was a significant decrease in mean arterial pressure ($P < 0.01$), but no change in heart rate, after the induction of anaesthesia. During and after surgery there were no significant differences in heart rate and mean arterial pressure between the two groups.

Haematocrit

The haematocrit decreased progressively throughout the study in both groups, from 40.7% to 36.9% ($P < 0.001$) after 6 h in the halothane patients and from 39.4% to 36.3% ($P < 0.001$) after 6 h in the fentanyl patients. There was no significant difference between the groups.

Pain evaluation

There was no significant difference in pain scores between the two groups 1, 2 and 4 h after the completion of surgery. In the halothane patients the scores were 4.2 (1.5–9.0), 3.4 (1.2–7.2) and 2.9 (0.7–8.3) and in the fentanyl

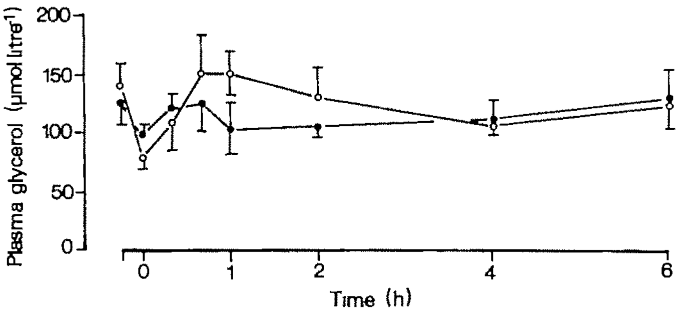

FIG. 6. Mean (±SEM) plasma glycerol (μmol litre^{-1}) concentrations in patients receiving halothane (solid circles) or fentanyl (open circles). Surgery started at 0 min.

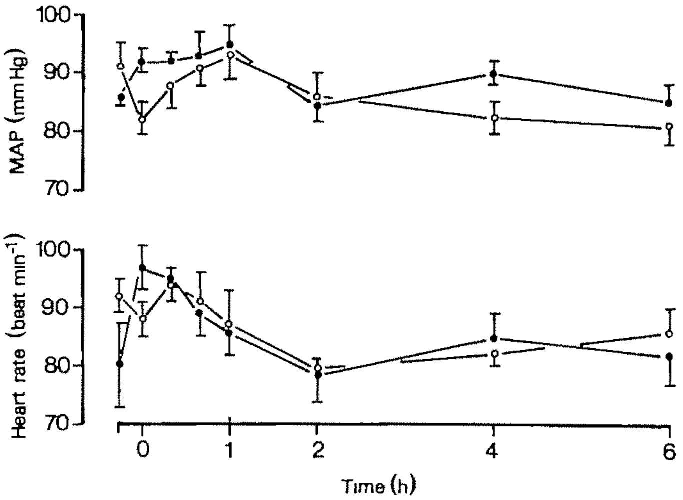

FIG. 7. Mean (±SEM) heart rate (beat min^{-1}) and arterial pressure (mm Hg) in patients receiving halothane (solid circles) or fentanyl (open circles). Surgery started at 0 min.

patients 4.6 (2.5–8.3), 3.0 (1.4–6.3) and 2.8 (2.2–7.6), respectively. The total dose of papaveretum given in the 24 h after surgery was 36 ± 3 mg in the halothane group and 42 ± 2 mg in the fentanyl group.

DISCUSSION

The results show that fentanyl 15 μg kg^{-1} prevented the β-endorphin, ACTH, GH, cortisol and glucose responses to pelvic surgery. Furthermore, inhibition of the secretion of the pituitary hormones persisted until at least 4 h after the start of surgery, whereas Dubois and colleagues (1982) found an increase in plasma β-endorphin concentration on awakening from anaesthesia. However, a direct comparison between the two studies is not possible because these workers used laparotomy as the surgical model and did not standardize either the dose of fentanyl (10–20 μg kg^{-1}) or the analysis of the data, which were grouped into "early" or "late" surgery.

Our finding of a similar pattern of change in plasma β-endorphin and ACTH values is not surprising as both peptides are derived from the same precursor molecule proopiomelanocortin. Although it is commonly assumed that changes in plasma β-endorphin concentration reflect changes in pituitary secretion, a contribution from peripheral tissues cannot be excluded as β-endorphin is also found in small amounts in organs such as the pancreas, gut and kidney (Grossman and Clement-Jones, 1983). The effects of fentanyl in inhibiting the GH as well as the ACTH and β-endorphin responses to surgery suggest that the changes in the circulating proopiomelanocortin-derived peptides found in this study are caused mainly by alterations in pituitary secretion.

The attenuation of the glycaemic response during surgery in patients who received fentanyl 15 μg kg^{-1} was surprising, as previous work suggested that a much greater dose was required (Hall et al., 1978). The increase in blood glucose concentration found during surgery is usually considered to be mediated mainly by the action of catecholamines, particularly adrenaline, in increasing glucose production by the liver (Hall, 1985). Strong evidence for this mechanism is provided by the ability of extradural analgesia, to a level which blocks the innervation of the adrenal medulla, to prevent the glycaemic response to surgery in the presence of the continuing secretion of other catabolic hormones (Kehlet, 1982). Although we did not measure plasma catecholamine concentrations in the present study, fentanyl had no effect on the intraoperative changes in the blood lactate, plasma glycerol, or plasma insulin concentrations, or on heart rate and arterial pressure—indices known to be influenced by increased sympathetic nervous system activity (Cooper et al., 1980; Walsh et al., 1982). It seems unlikely, therefore, that there was a major difference in catecholamine secretion between the groups and so other catabolic hormones may have been mediators, at least in part, of the glycaemic response.

Suppression of cortisol secretion in the fentanyl patients probably contributed towards the decreased glycaemic response, as Lacoumenta, Paterson and co-workers (1986) have shown that etomidate, which inhibits cortisol synthesis by an effect on the adrenal cortex, decreased blood glucose concentration by around 0.5 mmol litre^{-1} during similar surgery. A role for GH in mediating the glycaemic response is less likely, as Metcalfe and colleagues (1981) and Sherwin and co-workers (1983) failed to demonstrate an acute effect of GH on blood glucose concentration even when the hormone was infused to give a 10-fold increase in circulating values. The administration of large doses of β-endorphin i.v. is known to influence blood glucose concentration, either indirectly by modifying glucagon and insulin secretion, or by a direct effect on the liver (Feldman et al., 1983; Radosevich et al., 1984). It is conceivable, therefore, that the increased plasma β-endorphin concentration found during surgery contributes to the glycaemic response. We have shown recently, however, that when human β-endorphin is infused during surgery to achieve plasma values 100-fold greater than those observed in the present study, there is only a transient increase in blood glucose concentration (Lacoumenta, Yeo et al., 1986). This short-lived effect was associated with an increase in plasma glucagon concentration. Thus, the increase in β-endorphin found during surgery probably does not contribute significantly to the mobilization of glucose.

The increase in plasma glucagon concentration observed only in the fentanyl patients is of considerable interest. Morphine has a direct effect on the pancreas and stimulates the secretion of glucagon (Ipp, Dobbs and Unger, 1978; Ipp et al., 1980). It is probable, therefore, that fentanyl has a similar effect and while its use clinically is often associated with suppression of hypothalamic–

pituitary function, it may, paradoxically, stimulate the secretion of glucagon and, hence, tend to increase blood glucose concentration. In the present study there was no difference in plasma glucagon concentration between the fentanyl and halothane groups, but an investigation of the effects of high-dose fentanyl ($> 50\ \mu g\ kg^{-1}$) on pancreatic secretion may show a greater response.

A recent Editorial (1985) has drawn attention to the relatively small part played by analgesia in determining the endocrine and metabolic response to surgery. Our hormonal data lend further support to this supposition. Pain scores were similar in both groups 2 h after completion of surgery (approximately 4 h after start of surgery), but β-endorphin and ACTH values were much higher in the halothane patients (35 *v.* 14 pmol litre^{-1}, $P < 0.05$; 237 *v.* 129 ng litre^{-1}, ns, respectively). Plasma cortisol, which is commonly used to assess the "stress" of surgery, showed an even greater difference than ACTH, with plasma concentrations of 877 nmol litre^{-1} in the halothane group and 331 nmol litre^{-1} in the fentanyl patients ($P < 0.001$). Thus the patient's perception of pain is a poor guide to the magnitude of the hormonal changes.

In conclusion, fentanyl 15 $\mu g\ kg^{-1}$ inhibited the β-endorphin, ACTH, GH, cortisol and glucose response to pelvic surgery. Changes in circulating β-endorphin during surgery probably reflect alterations in pituitary secretion and appear to have no major metabolic effects. Other physiological effects of the hyperendorphinaemia of surgery remain to be elucidated.

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EFFECT OF I.V. LIGNOCAINE ON PAIN AND THE ENDOCRINE METABOLIC RESPONSES AFTER SURGERY

K. BIRCH, J. JØRGENSEN, B. CHRÆMMER-JØRGENSEN AND H. KEHLET

Apart from its extensive use in local anaesthesia, lignocaine may have other potential therapeutic uses as a result of its membrane stabilizing effect and ability to suppress irritable foci in various organs. Thus, the use of lignocaine in the treatment of ventricular arrhythmias and epileptic seizures is well documented. In addition, a protective effect on the ischaemic brain has been suggested because of the inhibition of oxygen and glucose consumption in the brain (Astrup, Skovsted et al., 1981; Astrup, Sørensen et al., 1981).

Potential advantages of i.v. lignocaine during anaesthesia and surgery have been suggested in regard to a decrease in anaesthetic requirements (Phillips et al., 1960; Himes, DiFazio and Burney, 1977), the production of stable clinical anaesthesia (Soares, 1952; Blancato, Peng and Alonsabe, 1969; Knight et al., 1980) and for relief of pain after surgery (de Clive-Lowe, Spencer Gray and North, 1954; Desmond, 1957; de Clive-Lowe, Desmond and North, 1958; Bartlett and Hutaserani 1961). However, the possible effect of i.v. lignocaine on postoperative pain has been supported mainly by uncontrolled observations. In a single controlled study on experimentally induced ischaemic pain, no effect was observed on pain threshold or tolerance at blood concentrations of 1–3 μg ml^{-1} (Rowlingson et al., 1980).

Therefore, the present study was undertaken to investigate, under controlled conditions, the possible effect of i.v. lignocaine on postoperative pain, and the adrenocortical and hyperglycaemic responses to abdominal hysterectomy.

SUMMARY

Pain intensity, and blood glucose and plasma cortisol concentrations were measured following abdominal hysterectomy in 18 patients allocated randomly to receive either i.v. lignocaine 1.5 mg kg^{-1} plus 2 mg kg^{-1} h^{-1}, or saline. The administration of lignocaine resulted in plasma concentrations between 1.5 and 2.0 μg ml^{-1} during the 2-h study period. However, the administration of lignocaine i.v. had no effect on the intensity of pain after surgery, or on the adrenocortical and hyperglycaemic responses to surgery.

PATIENTS AND METHODS

Eighteen otherwise healthy women undergoing elective abdominal hysterectomy were studied. Informed consent to participate was obtained from all patients and the design of the study was approved by the ethics committee of Copenhagen County Hospitals.

All patients received a general anaesthetic which included the administration of thiopentone, suxamethonium, pancuronium, and halothane and nitrous oxide in oxygen. Diazepam 0.2 mg kg^{-1} by mouth was used for premedication. Glucose was not given during the study. No analgesics were given during surgery.

The 18 patients were allocated randomly to receive, under double-blind conditions, either an i.v. injection of lignocaine 1.5 mg kg^{-1} as a bolus plus an i.v. infusion of 2 mg kg^{-1} h^{-1} for 2 h, or saline in the same volumes for injection and infusion. The administration of lignocaine or saline started following the first request for pain relief after surgery.

Age (mean 41 ± 2 yr in the lignocaine group, and 42 ± 2 yr in the saline group) and weight (62 ± 4 and 68 ± 3 kg, respectively) did not differ

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between groups ($P > 0.05$). All patients were without cardiovascular or hormonal diseases; none was receiving any medication, including contraceptives.

Blood samples were taken from a central vein just before extubation of the trachea and every 20 min until the patient requested pain relief. From this time blood samples were taken at 0, 10, 20, 30, 40, 60, 80, 100 and 120 min after the injection of, and the start of the infusion of, lignocaine or saline.

When the patients requested pain relief, pain intensity was measured using a 10-cm visual analogue scale at the same times as blood sampling. If the patients did not obtain any pain relief (i.e. the pain intensity score had changed less than 1 cm) 30 min after starting the lignocaine or saline infusion, the patients received morphine 0.15 mg kg^{-1} i.v. followed by a supplementary dose, if necessary.

The lignocaine–saline infusion, blood sampling and visual analogue pain scoring continued irrespective of the administration of morphine.

Blood glucose concentration was measured by a routine glucose oxidase method and cortisol concentration by a commercial radioimmunoassay. Plasma lignocaine concentration was measured by gas chromatography (by Dr Arne Hansson, Department of Clinical Chemistry, Malmö Allmänna Sjukhus, Malmö, Sweden).

Statistical analysis was performed using Student's *t* test for paired and non-paired variables. $P < 0.05$ was considered significant. All values are reported as mean ± SEM.

RESULTS

There was no difference between the lignocaine group and the saline group with regard to time from skin incision to extubation of the trachea (81 ± 3 and 86 ± 8 min, respectively) ($P > 0.05$) or in the time from extubation of the trachea to the first request for pain relief and, therefore, the start of the infusion of lignocaine or saline (37 ± 4 and 33 ± 6 min, respectively) ($P > 0.05$).

Similarly, no differences were observed in the administration of morphine between the lignocaine and saline groups (8.3 ± 0.7 mg supplemented with 3.9 ± 1.4 mg and 10.0 ± 0.7 mg supplemented with 5.7 ± 1.3 mg, respectively) ($P > 0.05$).

Pain intensity scores (mean ± SEM) in the two groups are shown in figure 1. In the saline group,

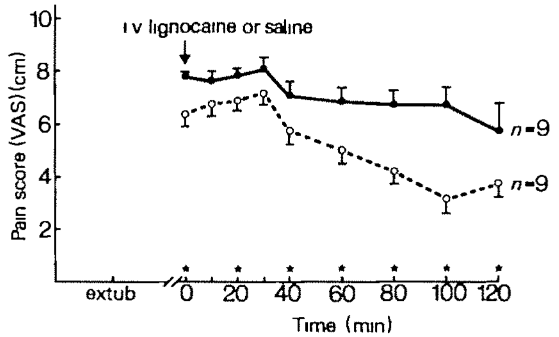

FIG. 1. Pain scores (mean ± SEM) during the first 120 min after abdominal hysterectomy in patients receiving either an i.v. injection of lignocaine 1.5 mg kg^{-1} plus an i.v. infusion of 2 mg kg^{-1} h^{-1} for 2 h (——) or saline (---). Patients who felt no pain relief 30 min after initiation of lignocaine or saline infusion received i.v. morphine 0.15 mg kg^{-1} followed by a supplementary dose if necessary. *Significant differences between groups ($P < 0.05$).

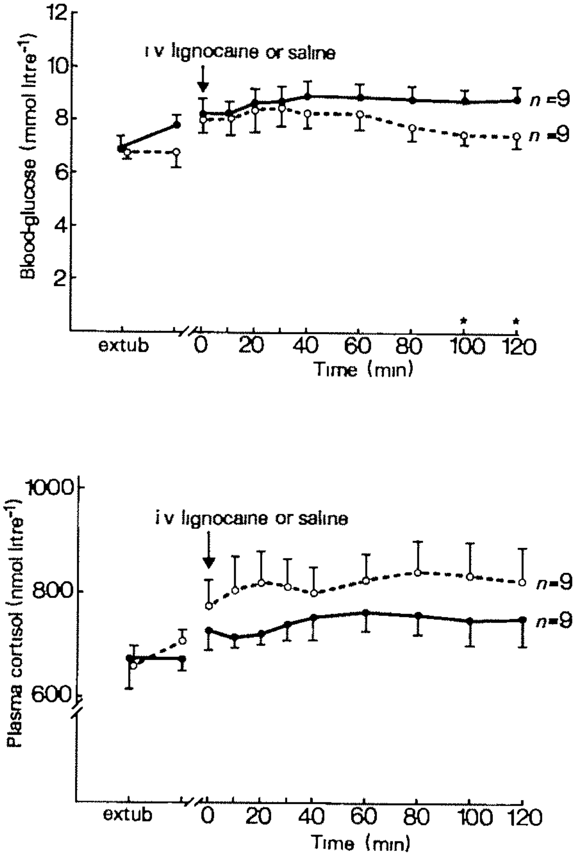

FIG. 2. Blood glucose and plasma cortisol concentrations (mean ± SEM) after abdominal hysterectomy; same procedure as figure 1. —— = Lignocaine; --- = saline. *$P < 0.05$.

pain scores were significantly lower than in the lignocaine group at the first request for pain relief and, therefore, on the initiation of the infusion of lignocaine or saline. However, during the first 30 min after the administration of lignocaine or saline, pain scores were constant in both groups. Thereafter, a slight decrease in pain intensity was observed in both groups following the administration of morphine. However, pain scores were higher in the lignocaine group than in the saline group throughout the study period.

Changes in plasma cortisol and blood glucose concentrations are shown in figure 2. Similar concentrations were observed following extubation of the trachea in both groups, and the administration of lignocaine or saline had no effect on the plasma concentrations of cortisol or glucose during the following 2 h. Plasma cortisol concentrations were slightly (but insignificantly) higher in the saline group and blood glucose concentrations lower 100 and 120 min after the start of infusion in the saline group compared with the lignocaine group ($P < 0.05$).

Plasma concentrations of lignocaine were between 1.5 and 2.0 $\mu g\ ml^{-1}$ (fig. 3).

No patient experienced any complications or side effects of the lignocaine injection and infusion.

DISCUSSION

It has been demonstrated previously in uncontrolled studies that i.v. lignocaine in doses of 400–1000 mg produces good pain relief after surgery (de Clive-Lowe, Spencer Gray and North, 1954; Desmond, 1957; de Clive-Lowe, Desmond and North, 1958; Bartlett and Hutaserani, 1961). However, in the present controlled double-blind study, no effect of i.v. lignocaine was observed on pain intensity at the time of first postoperative request for pain relief. Furthermore, the adrenocortical and hyperglycaemic responses were not influenced. The explanation for these discrepancies may be partly the different designs of the studies and partly the different dosages of lignocaine used as our patients received on average 350 mg of lignocaine compared with the 400–1000 mg given in the above-mentioned studies. However, if the administration of lignocaine was effective in the treatment of postoperative pain, there might be a risk of toxic symptoms with the higher doses. In our patients plasma concentrations of lignocaine were well below toxic values. It may be argued that, in our study, lignocaine was administered following a request for pain relief (in the postoperative period), in contrast to other studies in which the lignocaine was administered during the operation (de Clive-Lowe, Spencer Gray and North, 1954; Desmond, 1957; de Clive-Lowe, Desmond and North, 1958; Bartlett and Hutaserani, 1961). However, in another controlled study in which lignocaine (in doses between 250 and 730 mg) was administered during operation (Phillips et al., 1960), a significant reduction in anaesthetic requirement was observed, but no effect was demonstrated on the requirement for analgesics in the first 24 h after surgery. Pain intensity scores were not measured in that study.

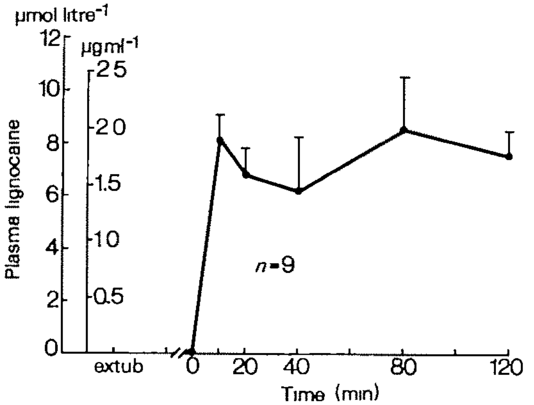

FIG. 3. Plasma lignocaine concentrations (mean ± SEM) after abdominal hysterectomy in patients receiving i.v. injection of lignocaine 1.5 mg kg^{-1} plus an i.v. infusion of 2 mg $kg^{-1}\ h^{-1}$ for 2 h.

The possible influence of i.v. lignocaine on other forms of acute pain has also been disappointing. Thus, lignocaine had no effect on pain threshold or pain tolerance to tourniquet-induced ischaemia when lignocaine plasma concentrations were 1–3 $\mu g\ ml^{-1}$ (Rowlingson et al., 1980). Similar results were found during the i.v. infusion of lignocaine under uncontrolled conditions in patients with neuralgic pain during tourniquet-induced pain when plasma lignocaine concentrations were less than 3 $\mu g\ ml^{-1}$ (Boas, Covino and Shahnarian, 1982). However, clinical pain before ischaemia was suppressed by lignocaine, and when plasma concentrations of lignocaine were higher both tourniquet pain and clinical pain were decreased (Boas, Covino and Shahnarian, 1982).

Although uncontrolled observations suggest that i.v. lignocaine infusion with plasma concentrations greater than 3 $\mu g\ ml^{-1}$ is beneficial in acute, including postoperative, pain, our double-blind controlled study failed to document any reduction in pain intensity or adrenocortical and hyperglycaemic responses to abdominal hysterectomy when plasma lignocaine concentrations were 1.5–2.0 μg ml^{-1}.

Although negative, our results may be of interest since there has been, in recent years, increasing interest in the systemic effects of the administration of lignocaine. Several studies have shown lignocaine to have some influence on the inflammatory response to injury on aspects of coagulation (thrombocyte aggregation) and in immunological function. We believe that some of these areas may very well be of clinical interest in the years to come.

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METABOLIC RESPONSE TO TOTAL HIP ARTHROPLASTY UNDER HYPOBARIC SUBARACHNOID OR GENERAL ANAESTHESIA

F. M. DAVIS, V. G. LAURENSON, J. LEWIS, J. E. WELLS AND W. J. GILLESPIE

SUMMARY

Whole blood glucose concentration was estimated in 93 patients undergoing total hip arthroplasty under either subarachnoid or general anaesthesia. In 77, plasma cortisol concentration was also estimated before and after surgery. There were no preoperative differences between the two groups. Blood glucose concentration increased slightly following induction in both groups, but with spinal anaesthesia it decreased again, whereas with general anaesthesia it continued to increase ($P < 0.0001$). Plasma cortisol concentration with spinal anaesthesia was 291 (SD 145) nmol litre^{-1} before, and 279 (253) nmol litre^{-1} 30 min after operation. With general anaesthesia there was a three-fold increase from 301 (159) nmol litre^{-1} (preoperative) to 987 (474) nmol litre^{-1} 30 min after operation ($P < 0.0001$). Low spinal anaesthesia with a predominantly unilateral block appears sufficient to suppress the neuroendocrine response to hip surgery.

Major surgery or trauma is accompanied by enhanced sympathetic activity and the release of trophic hormones from the hypothalamus, and with a failure of the normal negative feedback mechanisms of hormonal control (Hall, 1985). This results in cardiovascular, metabolic and other perturbations collectively known as "the stress response to surgery". Although general anaesthetic agents *per se* may have differing effects on autonomic tone and the secretion of hormones, these changes are minor compared with the response to surgery, and modify that response only slightly (Derbyshire and Smith, 1984).

Recent work has shown that extradural and subarachnoid anaesthesia can modify the response to lower abdominal and minor lower limb surgery (Engqvist et al., 1977; Pflug and Halter, 1981). Since it is known that the autonomic nervous system is involved in the activation of haemostasis (Small et al., 1984), modification of the neuroendocrine response to surgery by regional anaesthesia might alter the haemostatic response to surgery. We have reported differences in the intraoperative haemostatic response to total hip replacement surgery (THR) between subarachnoid and general anaesthesia (Davis et al., 1987). To see whether, in the same patients, the neuroendocrine response was also modified by subarachnoid anaesthesia, we studied the perioperative changes in plasma cortisol and blood glucose concentrations during THR.

PATIENTS, MATERIALS AND METHODS

Patients

One hundred and one patients gave written informed consent to the study, which was approved by the Hospital Ethical Committee. Of these, 93 provided venous blood samples for metabolic studies. Patients without a history of thromboembolic disease and presenting with osteoarthritis of the hip joint were studied.

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Aspirin, if being taken, was stopped 1 week before, and other analgesics on the day before, surgery. The sexes were separately randomized to receive either subarachnoid anaesthesia (SAB group) or general anaesthesia (GA group). The characteristics of the two groups are summarized in table I.

Clinical and anaesthetic management

Diazepam 10 mg was given orally as premedication, 90 min before the operation. Before induction, antiembolism stockings (TED, Kendall) were put on, electrocardiographic and arterial pressure monitoring commenced and an i.v. infusion established.

In the GA group, following fluid loading with acetated Ringer's solution, i.v. morphine 0.25 mg/kg body weight was given. Anaesthesia was induced with thiopentone, and neuromuscular blockade obtained with tubocurarine 0.5 mg kg^{-1}. The trachea was intubated and anaesthesia maintained with nitrous oxide in oxygen (2:1 ratio) with normocapnic intermittent positive pressure ventilation. Halothane, up to 1%, and incremental doses of tubocurarine were given as clinically indicated. At the end of surgery, any residual neuromuscular blockade was antagonized with neostigmine 2.5 mg (combined with atropine 1.2 mg).

For subarachnoid anaesthesia, fluid loading was commenced and the patient positioned lying on the non-surgical side with 10° head-down tilt. The subarachnoid space was identified using a routine sterile midline or paramedian approach at either the 3rd or 4th lumbar space. Anaesthesia was induced with a hypobaric solution of 1% amethocaine 10–15 mg, in sterile water. Light basal sedation was provided with morphine followed by an infusion of 0.8% chlormethiazole (Heminevrin). These patients breathed oxygen-enriched air throughout surgery. The aim of both anaesthetic techniques was to achieve modest hypotension for surgery.

An Exeter total hip arthroplasty was performed via the postero–lateral approach using a standard procedure without trochanteric osteotomy. Pressure injection of methylmethacrylate cement and a polyethylene femoral cement restrictor were used. During the operation the replacement of crystalloid and blood followed a strict regimen which was based on the duration of surgery, body weight, haematocrit and measured blood loss. Hypotension was managed with fluids and posturing alone. Vasoactive drugs were not used in the spinal anaesthetic solution or i.v. to manage hypotension—so as to avoid any possible interference with the biochemical or haematological studies.

In the SAB group, the height of the block on the surgical side was assessed, using temperature (cold) sensation, between 5 and 10 min following spinal injection, immediately before commencing the chlormethiazole infusion. This was to verify the adequacy of the block for surgery, rather than to provide accurate documentation of the spread of the block to its maximum extent. In the recovery room, at the end of surgery, the extent of blockade was again examined, when the ability to extend the knee against gravity and the presence or absence of light touch sensation in the L2/3 dermatome in both legs were noted.

Blood sampling

Venous blood samples were drawn from a fresh venepuncture site on four occasions: sample A = before induction of anaesthesia; sample B = 30 min after surgery started; sample C = 5 min after insertion of the femoral prosthesis; sample D = 30 min after the end of surgery.

On each occasion, as well as the samples for haematological studies (Davis et al., 1987), 0.5 ml of blood was placed into a micro glucose tube containing heparin fluoride for estimation of glucose concentration. Citrated platelet-poor plasma from samples A and D was obtained by centrifugation at 2550 *g* for 10 min at 4 °C and stored at −20 °C. Plasma cortisol concentration was estimated only if sufficient plasma was available for both this and the haematological tests.

Glucose and cortisol assays

Blood glucose concentration was measured using a standard automated immobilized hexokinase method (Technicon SMAC). The normal range for this laboratory is 3.5–8.0 mmol $litre^{-1}$ (random). Plasma cortisol concentration was estimated using a recently developed direct enzyme-linked immunosorbent assay (ELISA) (Lewis and Elder, 1985). The plasma cortisol concentration was corrected for citrate dilution. The normal range (08.00–12.00 h) for the assay in this laboratory is 110–770 nmol $litre^{-1}$ (Lewis and Elder, 1985).

Statistical analysis

The biostatistics package BMDP (Dixon, 1981) was used for statistical analysis. Analysis of covariance, paired and unpaired Student's *t* tests and linear regression analyses were used, where appropriate. The Bonferroni correction with repeated comparisons was applied to the blood glucose results such that significance was assumed where $\alpha = 0.017$.

RESULTS

There were no clinical differences between the two groups before surgery (table I). Blood transfusion was commenced between samples C and D in four of the SAB group and 11 of the GA group (Chi-square = 4.7; $P < 0.05$).

In the SAB group the degree of blockade was satisfactory throughout surgery in all but one patient who required light general anaesthesia for skin closure. At the time of the preoperative assessment the upper limit of blockade on the surgical side was between the L1 and T6 dermatomes, two-thirds being at T10 or below. The majority of patients still had some motor function in the non-surgical limb immediately before surgery, but sensation on the non-surgical side was not tested. At the end of surgery 87% of SAB patients were able to extend the knee against gravity and 76% had light touch sensation in the non-surgical limb whereas dense sensory and motor blockade persisted on the surgical side in all but one patient.

Plasma cortisol concentration

Plasma from samples A and D was available for cortisol examination in 77 of the 101 patients. Plasma cortisol concentrations before, and after, surgery are shown in figure 1. There was no difference between the groups before operation—SAB group 291 (145) nmol litre^{-1}; GA group 301 (159) nmol litre^{-1}. In the SAB group the mean cortisol concentration did not change following surgery (279 (253) nmol litre^{-1}), whereas there was a three-fold increase in the GA group (987 (474) nmol litre^{-1}) ($t = 10.93$, $P < 0.0001$). There was no correlation between the extent of the spinal blockade just before surgery and the postoperative plasma cortisol concentration.

TABLE I. *General data (mean, 1SD) for 93 patients undergoing total hip arthroplasty under either spinal (SAB) or general (GA) anaesthesia.* *P < 0.05

	SAB	GA
Patients		
Male	23	19
Female	24	27
Total	47	46
Age (yr)	66.6 (8.4)	65.1 (10.1)
Weight (kg)	71.3 (15.8)	69.2 (12.0)
Surgical time (min)	70.4 (10.2)	74.4 (17.6)
Patients transfused during operation	4	11*

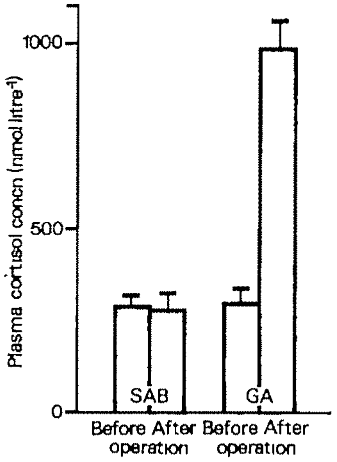

FIG. 1. Plasma cortisol concentrations (mean, SEM) pre-induction, and 30 min after surgery, in 77 patients undergoing total hip arthroplasty under either spinal (SAB, $n = 38$) or general (GA, $n = 39$) anaesthesia. See text for statistical analysis.

Blood glucose concentration

Data from all four samples A to D were obtained in 93 of the 101 patients studied. There was no difference between the two groups before induction (mean 5.3 (0.6) mmol litre^{-1}). The changes in blood glucose concentration are shown in figure 2. A slight increase was seen following the induction of anaesthesia in both groups. In the GA group blood glucose concentration continued to increase during surgery to achieve a mean value of 7.0 (1.1) mmol litre^{-1} in the early postoperative period (sample D), whereas it decreased significantly following the surgical procedure in the SAB group (5.8 (0.9) mmol litre^{-1}) (analysis of covariance: Time, $P < 0.0001$; Anaesthesia, $P = 0.18$; Time–Anaesthesia interaction, $P < 0.0001$). There was a significant difference in blood glucose concentration between the two groups at sample D ($t = 5.51$; $P < 0.0001$). In the SAB group there was no correlation between the upper limit of the block as tested just before surgery and the blood

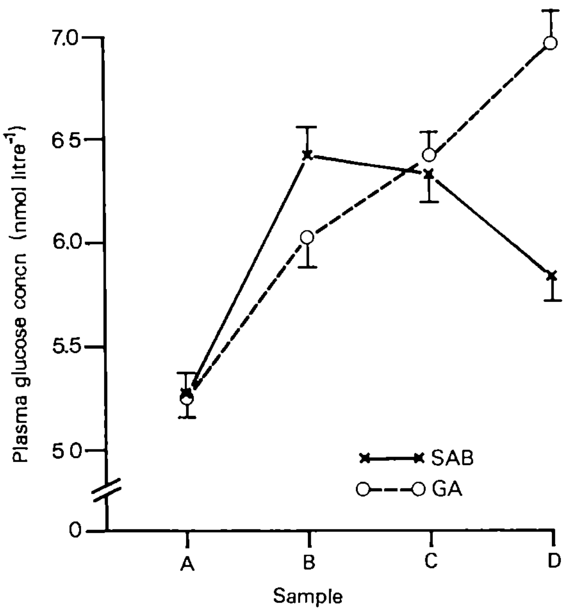

FIG. 2. Whole blood glucose concentrations (mean, SEM) in 93 patients during total hip arthroplasty under either spinal (SAB) or general (GA) anaesthesia. See text for timing of samples and statistical analysis.

glucose concentration at sample B. There were no differences in blood glucose concentrations between patients in whom blood transfusion was started before sample D and those who did not receive blood during this time.

DISCUSSION

The hormonal changes and systemic responses to trauma are dependent on an intact afferent innervation of the site of injury. This was first demonstrated in a limb burn model in dogs under general anaesthesia (Egdahl, 1959), in which denervation of the limb before the injury blocked the responses completely. Even denervation subsequent to the injury resulted in significant modification of the neuroendocrine response in this model.

In the clinical setting, extradural anaesthesia for abdominal hysterectomy has been shown to suppress the neuroendocrine response compared with general anaesthesia (Brandt et al., 1978), but this was only complete if the afferent blockade extended from T4 to S5 (Engqvist et al., 1977). In abdominal surgery, however, it is not only the extent of afferent blockade, but also the site and nature of the surgery that influences the metabolic response under regional anaesthesia. For instance, the cortisol response to upper abdominal surgery is not suppressed by segmental thoracic extradural blockade (Traynor et al., 1982), nor is that to Caesarean section by lumbar extradural blockade to T4 (Lindahl et al., 1983). The complex nature of the afferent innervation of the peritoneal cavity and its contents, combining autonomic (both sympathetic and parasympathetic) and somatic routes from widely different levels within the nervous system, presumably accounts for this marked variability.

Subarachnoid and extradural anaesthesia might be expected to have different effects since, in the latter, systemic uptake of the local anaesthetic, and of any vasoconstrictor agent used, could have direct effects of their own. However, in abdominal hysterectomy, the effects of subarachnoid anaesthesia appeared to be indistinguishable from those previously reported for extradural anaesthesia when compared with general anaesthesia (Moller et al., 1984). It is clear from these studies that regional anaesthesia does not modify the neuroendocrine response in a consistent fashion, and that different types of surgery, therefore, require separate assessment of this effect.

To study the neuroendocrine response to total hip replacement, and the haemostatic response (Davis et al., 1987) in the same patients, we compared subarachnoid, rather than extradural, anaesthesia with general anaesthesia in order to eliminate any systemic effects of the local anaesthetic agent. For the same reasons, vasoactive agents were not used in the spinal solution nor for the clinical management of any intraoperative hypotension.

Plasma cortisol concentration was measured at 30 min after operation because the increase has consistently been reported to be approaching its maximum at about 1–2 h following the start of surgery (Brandt et al., 1978). In the present study there was complete suppression of the cortisol response in the SAB group despite the fact that the upper limit of blockade in the majority of patients would have been no more than lower thoracic. This is quite different from the responses to abdominal hysterectomy reported previously (Brandt et al., 1978; Engqvist et al., 1977), and is consistent with Egdahl's experiments (Egdahl, 1959).

In a comparable study (Pflug and Halter, 1981), the neuroendocrine response to minor lower limb or perineal surgery involving minimal blood loss was studied in 34 patients under either general anaesthesia (with halothane) or spinal anaesthesia.

Plasma cortisol concentration increased steadily with general anaesthesia to peak in the early postoperative period, but did not change in the patients undergoing subarachnoid blockade. Despite the considerably more major surgical trauma and blood loss of total hip replacement in our own study compared with these patients, the changes in plasma cortisol concentration in the two studies, with a three-fold increase in the GA group and no change in the SAB group, are almost identical.

Blood glucose and adrenaline concentrations during and after surgery have been shown to correlate closely (Derbyshire and Smith, 1984). Pflug and Halter (1981) showed that there was a pronounced increase in plasma adrenaline concentration immediately following minor perineal or lower limb surgery under general anaesthesia, but that this did not occur following spinal anaesthesia. In the present study, an initial post-induction increase in blood glucose concentration occurred in both anaesthetic groups, suggesting that some sympathetic activation occurred over the pre-induction and induction period. This was transient in the SAB group and presumably related to the anxiety of undergoing a regional injection, whereas blood glucose concentration continued to increase in the GA group especially between samples C and D. The different patterns of change in blood glucose concentration observed in the present study in the two anaesthetic groups are consistent with the changes in adrenaline concentration reported in the patients studied by Pflug and Halter (1981).

In the present study, the extent of the block tended to be quite low and predominantly unilateral such that sympathetic blockade was not likely to be extensive in the majority of patients. However, since the height of the block was only tested on the surgical side within 5–10 min of spinal injection, this will not necessarily reflect its final cephalad spread. It is not surprising, therefore, that no correlation was found between this recorded level and the changes in blood glucose concentration.

The data presented in this study indicate that low hypobaric spinal anaesthesia with a predominantly unilateral block, unlike the extensive block required in lower abdominal surgery, is sufficient to suppress the plasma cortisol and blood glucose responses to total hip replacement. The modifications to the haemostatic response to hip surgery seen in these patients (Davis et al., 1987) are consistent with a difference in autonomic activity between the two anaesthetic techniques. Although, in patients undergoing abdominal hysterectomy (Rem et al., 1981), haemostatic changes have been reported to be independent of the neuroendocrine response to surgery, this may not be entirely the case with major lower limb surgery. This is presumably a result of the difference in autonomic innervation of the viscera of the peritoneal cavity compared with that of the tissues of the lower limb.

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CALCIUM AND MAGNESIUM CONTENT OF SKELETAL MUSCLE

Studies in Subjects Undergoing Diagnostic Testing for Malignant Hyperthermia

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SUMMARY

Ca^{2+} and Mg^{2+} contents were measured and compared among three different malignant hyperthermia susceptible (MHS) diagnostic groups. No difference was found among mean values for Ca^{2+} content, whereas Mg^{2+} content was greater in MHS muscle. Variance of measured values was unequal and greatest among MHS muscles, suggesting a possible abnormal distribution associated with MHS. Although more muscle fibres with $Ca^{2+} \leqslant 12$ μmol g^{-1} were observed in MHS muscle, this difference was not statistically significant. In contrast, non-parametric analysis showed that the population of Mg^{2+} values was significantly greater in the MHS muscle. This study suggests that the distribution of Ca^{2+} and Mg^{2+} values is different in MHS muscle as a result of unknown genetic factors associated with the disease.

Although the aetiology of malignant hyperthermia (MH) remains unresolved, current theory favours a defect in skeletal muscle (Kalow et al., 1970; Moulds and Denborough, 1974). One typical observation is that the *in vitro* contracture responses to halothane and to caffeine are abnormal in MH skeletal muscle (Nelson, Flewellen and Gloyna, 1983), and this has drawn attention to a possible defect in Ca^{2+} regulation in the MH muscle cell. Malignant hyperthermia occurs also in genetically predisposed pigs and many of the abnormalities observed in human MH muscle are found also in pig muscle (Nelson, Flewellen and Gloyna, 1983).

In MH susceptible pigs, total Ca^{2+} and Mg^{2+} content of skeletal muscle is lower than that in normal pigs (Nelson et al., 1974). Another study (Britt et al., 1975) reported that Ca^{2+} content was lower in MH pig and human skeletal muscle than in normal muscle. A subsequent study (Bennett et al., 1977) reported no differences in Ca^{2+} and Mg^{2+} content between MH and control human muscle. It has also been demonstrated that the Ca^{2+} content and contractility of MH pig muscle can vary with *in vitro* Ca^{2+} concentration and that this also differs from normal pig muscle (Nelson and Chausmer, 1981). Because of apparent contradictions in the literature regarding a content of Ca^{2+} in MH human skeletal muscle, and the obvious lower content of Ca^{2+} in MH pig muscle, we measured and compared Ca^{2+} and Mg^{2+} contents in skeletal muscle of human subjects undergoing diagnostic contracture testing of skeletal muscle.

SUBJECTS AND METHODS

Subjects were referred for diagnosis to our laboratory because of one or more anaesthetic occurrences in the family which raised the question of susceptibility to malignant hyperthermia. Biopsies of vastus lateralis were obtained at *in situ* resting length in special muscle biopsy clamps which contained muscle strips 2.5 cm long, 2.0 cm wide and 0.5 cm thick. Subjects were

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premedicated with diazepam 0.2 mg kg^{-1} orally and morphine 0.1 mg kg^{-1} i.m., and anaesthesia was provided by either general (thiopentone 4–5 mg kg^{-1}; fentanyl 0.005 mg kg^{-1} and diazepam 0.1–0.15 mg kg^{-1}), or by subarachnoid anaesthesia (amethocaine). Informed consent to take muscle for research purposes was obtained from each subject and the study was approved by the Institutional Review Board at The University of Texas Medical Branch at Galveston.

Muscle fascicles, approximately 2 cm long and 2 mm diameter were dissected from the muscle clamp and used for *in vitro* diagnostic contracture testing. The standard diagnostic procedure in this laboratory is to treat two fascicles each to one of the three following tests: (1) 3% halothane, (2) cumulative caffeine doses, and (3) cumulative caffeine doses in the presence of halothane. Before one of these treatments, each fascicle is optimized for length/twitch tension in a Krebs–Ringer solution maintained at 37 °C. This diagnostic procedure differs from that of the European MH Group (The European Malignant Hyperpyrexia Group, 1984), which exposes muscle to only two treatments, caffeine alone and halothane alone, and a dynamic as well as static test is performed. As with our diagnostic results, the European MH Group also experiences MH equivocal patients but, basically, we diagnose the MH unequivocal patients by very similar tests. At least two fascicles, not used for contracture tests, were taken for Ca^{2+} and Mg^{2+} analysis. During the dissection, the muscle biopsy was incubated in Krebs–Ringer solution containing Ca^{2+} 2.5 mmol $litre^{-1}$ at 25 °C and each fasicle used for cation analysis was dipped and blotted three times in Ca^{2+}-free Krebs–Ringer to remove contaminating Ca^{2+}. After dry weights had been determined, each fascicle was digested in 2 ml of HNO_3:$HClO_3$, 1:1, at 120 °C for 1 h. The digest was diluted to 10 ml in a final concentration of 1% $LaCl_3$. Calcium was analysed in a 1:25 dilution of the digest in 1% $LaCl_3$, while Mg^{2+} was diluted 1:250 in distilled water. Calcium and Mg^{2+} were determined by atomic absorption spectrophotometry.

Data were evaluated statistically as follows. Analysis of variance was used to partition and compare variance components. Differing variance structure and patterns among diagnostic groups indicated the use of a non-parametric test. The Kolmogorov–Smirnov two-sample test (Conover, 1980) was used to test for pairwise differences among diagnostic outcome groups.

RESULTS

The *in vitro* MH diagnostic test produces three contracture phenotypes in our laboratory (Nelson, Flewellen and Gloyna, 1983) and subjects in this study fell into one of these diagnostic groups. The *in vitro* contracture responses for each group are listed in table I. Phenotype H is an unequivocal diagnostic response and muscle from these individuals has abnormal contracture responses to each of the three following tests: 3% halothane, caffeine and the combination of 1% halothane plus caffeine. Phenotype negative (N) is an unequivocal diagnosis and the *in vitro* contracture responses are typical for control human skeletal muscle. Phenotype K, an equivocal diagnosis, is muscle that has normal contracture responses to halothane alone and to caffeine alone, but the contracture response to caffeine plus halothane is similar to responses for phenotype H muscle.

Descriptive statistics for the Ca^{2+} content of skeletal muscle among the diagnostic groups showed only small differences in mean values (table II), but coefficients of variation disclosed marked differences among the three diagnostic groups. For example, total variability for Ca^{2+} content for phenotype H muscle was significantly

TABLE I. In vitro *malignant hyperthermia diagnostic contracture values among outcome groups. N = Negative; K = equivocal; H = unequivocal diagnosis (see text) CSC = Caffeine specific concentration calculated to produce 1 g isometric contracture; HCSC = calculated caffeine specific concentration required to produce 1 g isometric contracture in the presence of 1% halothane*

Phenotype	n	CSC (mmol $litre^{-1}$)	HCSC (mmol $litre^{-1}$)	3% Halothane contracture (g)
N	11	7.69 ± 4.40	1.30 ± 0.42	0.29 ± 0.23
K	26	5.01 ± 1.17	0.65 ± 0.20	0.32 ± 0.24
H	14	2.73 ± 1.88	0.41 ± 0.33	2.54 ± 1.06

TABLE II. *Descriptive statistics for Ca^{2+} and Mg^{2+} content of human skeletal muscle from malignant hyperthermia diagnostic groups. † Variation among all fascicles. ‡ (SD/Mean) × 100*

Cation	Diagnostic phenotype	No. of subjects	No. muscle fascicles	Mean	SD†	Coeff. of variation‡ (%)
Ca^{2+}	H	14	44	16.71	8.05	48.2
Ca^{2+}	K	26	69	17.20	5.09	29.6
Ca^{2+}	N	11	46	17.11	4.41	25.8
Mg^{2+}	H	14	44	38.38	10.77	28.1
Mg^{2+}	K	26	65	36.21	9.89	27.3
Mg^{2+}	N	11	46	32.89	6.21	18.9

TABLE III. *Analysis of variance and variance component estimation for Ca^{2+} and Mg^{2+} content of skeletal muscle from three malignant hyperthermia diagnostic groups. † Variance for subjects has been corrected (subtracted) for variance of fibres. The % is of total variance*

Cation	Diagnostic phenotype	Source	d.f.	Mean Square	Variance component (%)†
Ca^{2+}	H	Subjects	13	108.5	20.5 (30.9)
		Fascicles	30	45.8	45.8 (69.1)
Ca^{2+}	K	Subjects	25	46.1	12.2 (46.4)
		Fascicles	43	14.1	14.1 (53.6)
Ca^{2+}	N	Subjects	10	43.6	7.6 (37.7)
		Fascicles	35	12.5	12.5 (62.3)
Mg^{2+}	H	Subjects	13	153.4	17.5 (14.9)
		Fascicles	30	99.9	99.9 (85.1)
Mg^{2+}	K	Subjects	25	105.3	5.0 (5.1)
		Fascicles	39	93.0	93.0 (94.9)
Mg^{2+}	N	Subjects	10	50.6	3.8 (9.7)
		Fascicles	35	35.1	35.1 (90.3)

greater than that for phenotype N muscle ($P = 0.0001$). Means for Mg^{2+} content showed more separation across diagnostic groups than those for Ca^{2+}, but were not significant ($P = 0.0686$) by the classical F test (incorporating both subject and fibre error). However, this P value is difficult to interpret as a result of the disparate variances of the three groups (table II). To study further the variance structure among these diagnostic groups, variance components for subject-to-subject and for fibre-to-fibre variability were estimated for the three diagnostic groups using analysis of variance (table III).

Evaluation of these partitioned variance components revealed two distinct and unexpected patterns. First, fascicle-to-fascicle variability was greater than subject-to-subject variability—a result that is generally opposite to that observed for most biological systems. Second, when considering the actual variance component (VC) values for Ca^{2+} measurements, phenotype H subjects were the most variable ($\sqrt{\text{subj.VC}} = 4.53\ \mu mol\ g^{-1}$) compared with phenotypes K ($\sqrt{\text{subj.VC}} = 3.49\ \mu mol\ g^{-1}$) and N ($\sqrt{\text{subj. VC}} = 2.76\ \mu mol\ g^{-1}$). Although fascicle-to-fascicle variability was greater than subject-to-subject variability for Ca^{2+} measurements, subject variability was an important factor as it accounted for 30.9%, 46.4% and 37.7% of the variability for phenotypes H, K and N, respectively. In contrast, subject-to-subject variability for Mg^{2+} measurements contributed only 14.9%, 5.1% and 9.7% of total variance for the H, K and N groups, respectively. Thus, when muscle Mg^{2+} content is measured, variation among subjects within diagnostic groups is unimportant relative to the fascicle-to-fascicle variability. Similar to the patterns observed for Ca^{2+} measurements, the subject-to-subject and fascicle-to-fascicle variability for Mg^{2+} was greater in phenotypes H and K when compared with phenotype N (table III).

The unequal variances among diagnostic groups precluded the use of the F statistic. For this

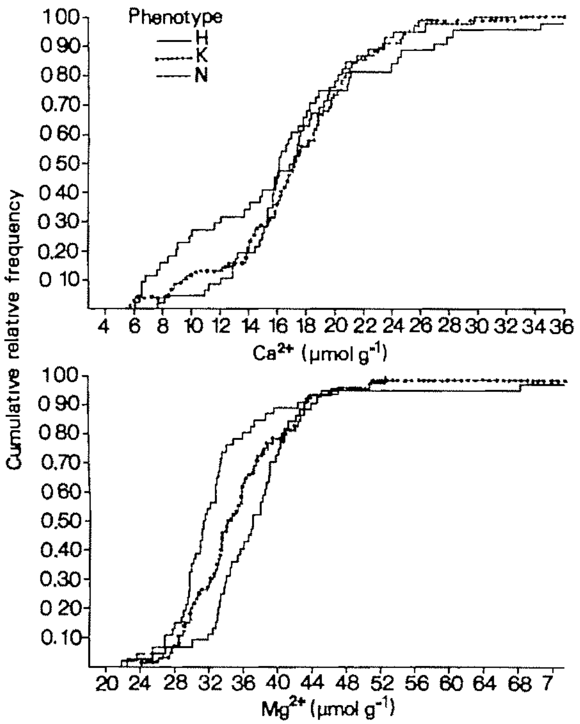

FIG. 1. The cumulative relative frequency distributions for Ca^{2+} and Mg^{2+} content in human skeletal muscle of malignant hyperthermia diagnostic phenotypes. Malignant hyperthermia diagnostic contracture phenotypes H (susceptible) and N (non-susceptible) are unequivocal. The susceptibility of phenotype K is equivocal.

reason, the non-parametric Kolmogorov–Smirnov two-sample test (Conover, 1980) was applied. This test statistic utilizes the absolute value of the maximum difference between the cumulative distribution functions as the test statistic. Cumulative distributions for each phenotype were plotted for Ca^{2+} and Mg^{2+} measurements (fig. 1), and results of the pairwise statistical comparisons for these distribution functions between diagnostic groups are presented in table IV. Statistically significant differences were not observed for Ca^{2+} among the three diagnostic phenotypes. Calcium values for phenotype H tended to be lower than those for K and N, with approximately 30% of the values being less than 12 μmol g⁻¹. In comparison, only 13% and 9% of phenotypes K and N, respectively, had values less than 12 μmol g⁻¹.

No statistically significant difference was found for Mg^{2+} between phenotypes H and K, although a trend for the values to separate was observed ($P = 0.1246$). Magnesium content of phenotypes H and K were each significantly different ($P < 0.0029$) from phenotype N.

DISCUSSION

The average skeletal muscle content of Ca^{2+} and Mg^{2+} did not differ significantly among the three diagnostic groups in this study. This result is consistent with the conclusions of a study reported by Bennett and colleagues (1977), but disagrees with the results reported by Britt and co-workers (1975). An obvious conclusion from the previous studies (Britt et al., 1975; Bennett et al., 1977) and the present study is that discrimination of normal from malignant hyperthermia susceptible muscle is not possible simply by measuring the total muscle content of Ca^{2+} and Mg^{2+}. In the study reported by Bennett and colleagues (1977), histograms revealed considerable spread in the values for Ca^{2+} content in both normal and MH muscle, but with an apparent larger spread in MHS *v.* normal muscle values. Our data have similar patterns of variability and we addressed the possibility that the greater fascicle-to-fascicle

TABLE IV. *Pairwise comparisons for Ca^{2+} and Mg^{2+} muscle content among phenotypes H, K and N by the Kolmogorov–Smirnov two-sample test.* † *Large sample approximation* (n_1, $n_2 > 40$) *of two-tailed levels of significance (Bradley, 1968)*

Cation	Comparison between diagnostic phenotypes	Number of observations n_1, n_2	Value at maximum difference (μmol g⁻¹)	P†
Ca^{2+}	H *v.* K	44, 69	12.09	0.2994
	H *v.* N	44, 69	10.02	0.1891
	K *v.* N	69, 46	16.22	0.5587
Mg^{2+}	H *v.* K	44, 65	36.34	0.1246
	H *v.* N	44, 46	33.19	<0.0001
	K *v.* N	65, 46	33.19	0.0029

variance in Ca^{2+} and Mg^{2+} content observed in MHS muscle could reflect an abnormality. In most biological systems, experimental units (diagnostic subjects, in our study) generally represent a larger source of variability, while measurements on replicate samples from each subject (muscle fascicles, in our study) are associated with less variability. This variability in Ca^{2+} and Mg^{2+} content of muscle was greater in the MHS muscles and one possible explanation is that some MHS fibres may be low in Ca^{2+} and high in Mg^{2+} content, while others may have normal concentrations of these cations. A previous study in MHS pigs (Nelson and Schochet, 1982) produced results that suggest the type I myofibres have the MH defect while type II myofibres may be less defective, or they may be normal. If the MH defect is limited to type I myofibres, this could be related to the variance patterns observed for Ca^{2+} and Mg^{2+} content values among the diagnostic groups.

Another possible explanation is that MH is inherited as a multifactorial trait and that the greater variance in measurements of cation content of MH muscle is attributable to genetic factors. The MHS pigs with lower muscle content of Ca^{2+} and Mg^{2+} represent a more genetically homogeneous group than do the MH diagnostic patients studied. It is possible that some MH families have a genetic predisposition towards lower Ca^{2+} and higher Mg^{2+} concentrations in their muscle than do other MH families. The number of single family members in our study is too small to allow a comparison.

A study with more refined measurements of Ca^{2+} and Mg^{2+} content in single muscle fibres identified by fibre typing is necessary to determine whether a subpopulation of muscle fibres exists among MH muscles, or whether there is a subpopulation of MH subjects in whom the skeletal muscle content of these cations is lower.

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EFFECTS OF H-2 ANTAGONISTS ON THE ELIMINATION OF BUPIVACAINE

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SUMMARY

The effects of two histamine H-2 antagonists, cimetidine and ranitidine, on the elimination of bupivacaine were studied in four male volunteers. The cimetidine-treated group demonstrated a statistically significant decrease in clearance of bupivacaine. These results indicate that concomitant administration of cimetidine and bupivacaine may increase the likelihood of toxicity of the latter agent.

Prophylactic administration of H-2 antagonists has been advocated to reduce the probability and sequelae of aspiration of gastric contents (Moir, 1983; Johnston et al., 1983; McAuley et al., 1983), and a survey, conducted in 1984, of obstetric units in the United Kingdom, revealed that approximately 15% utilized H-2 antagonists as part of their prophylactic regimen for parturients in active labour (Sweeney and Wright, 1986). However cimetidine and, to a lesser extent, ranitidine have been shown to reduce drug elimination by the liver through a reduction in liver blood flow and by inhibition of microsomal enzymes (Somogyi and Gugler, 1982; Kirch, Hoensch and Janisch, 1984). These effects have led to interactions with some co-administered drugs, most notably lignocaine (Feely et al., 1982; Knapp et al., 1983; Wing et al., 1984; Robson et al., 1985).

Despite reports of its serious toxicity (Marx, 1984; Scott, 1984), bupivacaine continues to be the local anaesthetic agent used most frequently for extradural analgesia, and since large numbers of obstetric patients may be exposed simultaneously to H-2 antagonists and bupivacaine, we investigated this potential drug interaction.

SUBJECTS AND METHODS

Ethics Committee approval was sought and obtained for this double-blind, randomized crossover investigation, in which four healthy male volunteers took part. The minimum period between observations in any one subject was 1 week.

Placebo, cimetidine 400 mg or ranitidine 150 mg was administered by mouth at 22.00 h on the evening before the study and at 08.00 h on the study day. Three hours later bupivacaine 50 mg was infused over 15 min by means of a syringe pump. Venous blood was sampled from the contralateral arm at the conclusion of the infusion and at 30, 60, 120, 180, 240 and 300 min thereafter. The samples were immediately centrifuged and the separated plasma frozen at −70 °C until required for assay. Plasma bupivacaine concentrations were determined by gas–liquid chromatography.

Chromatography

Purified nitrogen 30 ml min^{-1} was used as carrier gas. The injection port and nitrogen phosphorous detector (NPD) were maintained between 250 and 265 °C, and the temperature of the 1.8-m glass column (2 mm diameter) packed with 5% OV17 on GCQ 100–120 mesh was 260 °C. The voltage for the NPD head was 16–19 V.

Pharmacokinetic analysis

Plasma concentration–time data for individual subjects were analysed by non-linear regression using the computer program AUTOAN (Sedman and Wagner, 1977). The terminal elimination rate

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constant (β) was calculated from the terminal slope of the concentration of the log-linear phase of the concentration–time curve. The elimination half-life was calculated using the equation:

$$T_{\frac{1}{2}} = 0.693/\beta$$

The area under the plasma concentration–time curve (AUC) was calculated from the linear trapezoidal method by the addition of

$$\mathrm{AUC}_{0\text{–}315\,\mathrm{min}}$$

to the extrapolated value to infinity:

$$(\mathrm{concn}_{315\,\mathrm{min}})/\beta$$

Total body clearance (*Cl*) was calculated using the equation:

$$Cl = \mathrm{Dose}/\mathrm{AUC}$$

and the apparent volume of distribution ($V\mathrm{D}$) from

$$V\mathrm{D}_{\beta} = \mathrm{Dose}/\beta.\mathrm{AUC}$$

Statistical analysis was performed using Friedman's non-parametric two-way analysis of variance, followed by Wilcoxon's test based upon the difference in rank sums between any two treatments.

RESULTS

The effects of the histamine H-2 antagonists cimetidine and ranitidine on the pharmacokinetic parameters of i.v. bupivacaine are summarized in table I. Cimetidine significantly increased the area under the concentration–time curve (AUC), that is to say it decreased the clearance of bupivacaine, whereas ranitidine had no significant effect.

No significant effect of either drug was detected on either the elimination half-life or the apparent volume of distribution of bupivacaine.

The individual AUC values recorded from three study groups are illustrated in figure 1. The four subjects treated with cimetidine showed a mean increase of 40% in AUC over the control value. Ranitidine pretreatment also enhanced the mean AUC value, by 25%; this was not statistically significant.

TABLE I. *Pharmacokinetic parameters (mean ± SD) of bupivacaine following i.v. infusion* (n = *4*). *P = *0.005 (Friedman non-parametric two-way analysis of variance)*

	Control	Cimetidine treated	Ranitidine treated
AUC (mg litre^{-1} min^{-1})	125 ± 48	172 ± 60*	151 ± 45
Cl (ml min^{-1})	450 ± 173	318 ± 108*	353 ± 102
$T_{\frac{1}{2}}$ (min)	113 ± 28	199 ± 140	147 ± 112
$V\mathrm{D}$ (litre)	74 ± 36	79 ± 29	63 ± 33

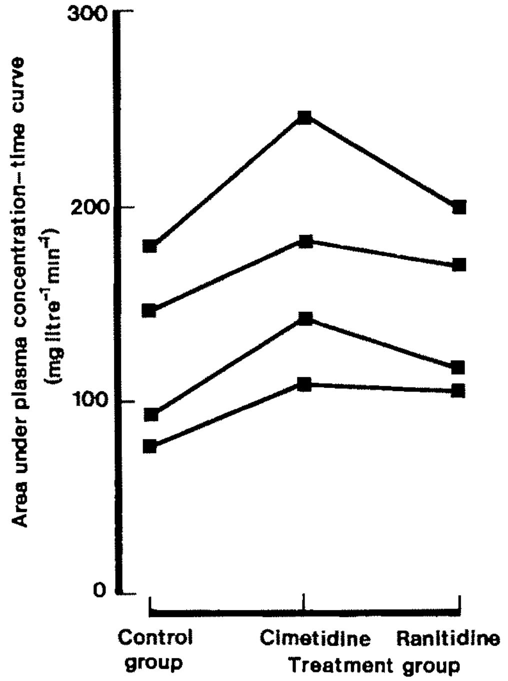

FIG 1. Plasma concentration–time curves of four subjects receiving bupivacaine 50 mg i.v.

DISCUSSION

The effects of cimetidine, and to a lesser extent ranitidine, on plasma concentrations of bupivacaine were qualitatively similar to those observed in other studies, including those involving lignocaine, another commonly used local anaesthetic agent (Feely et al., 1982; Feely and Guy, 1983; Knapp et al., 1983). Since bupivacaine exhibits a much lower hepatic extraction ratio than lignocaine (Tucker et al., 1977), the cimetidine-induced reduction in systemic clearance which we observed is more likely to have resulted from an effect of the H-2 antagonist on the oxidative metabolism or protein binding of bupivacaine, rather than any alteration in liver blood flow (Wilkinson and Shand, 1975). However, cimetidine is less than 20% bound to plasma proteins and is not considered to displace other drugs from plasma protein binding sites (Serlin, 1982). An effect of cimetidine on the metabolism of bupivacaine is therefore the most likely explanation of the observed interaction.

Substantial numbers of pregnant women may be exposed to both bupivacaine and cimetidine, and results obtained in this study lend support to the possibility of a clinically significant interaction with an increased likelihood of bupivacaine toxicity. The choice of ranitidine as an alternative H-2-antagonist may provide a solution, although interaction between bupivacaine and ranitidine has already been documented (Wilson et al., 1986).

Further work is required on the population that may be most at risk: parturients who receive large cumulative doses of bupivacaine for pain relief during labour and may then receive a substantial and potentially toxic dose for Caesarean section (Thorburn and Moir, 1984). This potential problem may be exacerbated by cimetidine, and requires clarification.

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QUANTITATIVE EEG ANALYSIS DURING ANAESTHESIA WITH ISOFLURANE IN NITROUS OXIDE AT 1.3 AND 1.5 MAC

H. SCHWILDEN AND H. STOECKEL

The rational and efficient use of EEG monitoring devices in the perioperative period requires a body of data which characterizes those EEG changes expected during anaesthesia. Although isoflurane has been studied intensively in the past decade, only a few studies (Brandt and Pokar, 1984; Clark et al., 1973; Dworacek and De Vlieger, 1984; Eger, Stevens and Cromwell, 1971; Poulton and Ellingson, 1984) considered the EEG changes associated with isoflurane anaesthesia. Moreover, much of the available information is qualitative, or semiquantitative, rather than of a quantitative nature.

The purpose of this study was to evaluate the EEG during clinical anaesthesia with isoflurane and nitrous oxide (in oxygen) at 1.3 and 1.5 MAC, and to study the distribution of various spectral EEG variables during surgery, and in the perioperative period.

PATIENTS AND METHODS

Fourteen patients without apparent neurological deficit participated in the study. They were randomly allocated to two groups ($n = 7$) anaesthetized with isoflurane plus 60% nitrous oxide (in oxygen) at 1.3 and 1.5 MAC. Assuming additivity of the MAC concept (Teplick, 1984), and taking 60% nitrous oxide as 0.6 MAC, the actual alveolar concentrations of isoflurane aimed at were 0.7 and 0.9 MAC, respectively. For the patients investigated we assumed 1 MAC of isoflurane to be 1.15 vol% (Stevens, Dolan and Gibbons, 1975).

SUMMARY

In 14 patients undergoing elective surgery the EEG was studied during anaesthesia with isoflurane and nitrous oxide (in oxygen) at 1.3 and 1.5 MAC. The distributions of spectral EEG indices of the baseline EEG, during the intraoperative and recovery periods were established and compared. Median frequency exhibited the most clear separation between the distributions during recovery and the intraoperative period. During anaesthesia, the median values were found to be lower than 5 Hz; when the patient was conscious, the EEG median frequency values were greater than 6 Hz. Time to recovery was 13.4±2.9 min and 30.0±8.5 min for the groups treated with 1.3 and 1.5 MAC, respectively. Burst suppression was observed during the loading period in all patients treated with 1.5 MAC and in five patients out of seven receiving 1.3 MAC. The average duration of the period of burst suppression was markedly greater in the group receiving 1.5 MAC than in the group receiving 1.3 MAC. It is concluded that devices designed for EEG trend monitoring during anaesthesia should preferably depict a frequency measure, and allow for burst suppression recognition before spectral analysis.

Anaesthetic procedure

Anaesthesia was induced with thiopentone 5 mg/kg body weight. Pancuronium and suxamethonium were administered. Once the trachea had been intubated, anaesthesia was maintained with 60% nitrous oxide and isoflurane in oxygen. Isoflurane was administered according to a scheme based on pharmacokinetic considerations consisting of an initial loading period of 15 min, followed

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by a lower vaporizer setting for the following 105 min which again was decreased if isoflurane was administered for longer than 2 h. This regimen led to almost constant end-tidal (Normac (Datex)) concentrations after 25–30 min (Schwilden et al., 1985). The data of the pharmacokinetic model (Davis and Mapleson, 1981; Lowe and Ernst, 1981) were individualized by estimating cardiac output, lean body mass and fat tissue from body weight and body height (Fiserova-Bergerova, Vlach and Casady, 1980).

Table I presents for both groups the demographic data as well as the durations of the administration of isoflurane and the times between intubation and extubation. End-tidal $P\text{CO}_2$ tension was measured breath-by-breath (Capnometer 47210A, Hewlett-Packard) and ventilation was adjusted to maintain the end-tidal $P\text{CO}_2$ between 4.5 and 4.8 kPa. Fresh gas flow was at least 0.5 litre min^{-1} greater than minute ventilation. Body temperature was kept greater than 36 °C.

Surgery was commenced not earlier than 15 min after the loading period, that is 30 min after the start of the isoflurane. At the end of surgery 100% oxygen was administered and neuromuscular blockade was antagonized with neostigmine. During the recovery period patients were frequently asked to respond to verbal commands.

EEG analysis

The information from four EEG leads (C_z–F_i, C_z–O_i, i = 1, 2) was recorded on magnetic tape (PR 2200, Ampex). One of the two symmetrical leads C_z–O_i(i = 1 or 2) was used for off-line signal analysis. The primary filter settings of the EEG amplifier (Mingograph Junior, Siemens) were 0.3 s and 70 Hz. For automatic analysis, the raw signal was filtered between 0.5 and 32 Hz and broken down into epochs of 8.192 s duration which were digitized at a rate of 125 Hz and 12 bit A–D resolution. For each epoch a set of eight EEG variables was calculated from the power spectrum between 0.5 and 32 Hz. Since the area under the power spectrum curve is proportional to the square of the mean amplitude (Bendat and Piersol, 1971), one may normalize the area under the power spectrum to one (normalized power spectrum) by extracting mean amplitude. Thus the entire dependence on absolute power of all EEG variables derived from the power spectrum can be focused on one quantity. From the normalized power spectrum the percentage of power in the frequency bands 0.5–2, 2–5, 5–8, 8–13 and 13–32 Hz was calculated as well as the median frequency—defined as the median (50% quantile) of the power spectrum regarded as a distribution (Schwilden and Stoeckel, 1980) and the 95% quantile (Hudson et al., 1983). Burst suppression was detected by an algorithm based on the local variance of the EEG signal before Fourier transformation and data smoothing. The duration of the period of suppression was expressed as a percentage of the duration of the total epoch. Artefact rejection was performed by visual inspection. For data smoothing a moving average over nine epochs was used.

TABLE I. *Demographic data and basic anaesthetic management (mean ± SD) of the patients treated with 1.3 and 1.5 MAC.*
†Maintenance concentration of isoflurane vaporizer setting

	1.3 MAC	1.5 MAC
Age (yr)	40.7	38.3
	14.0	16.2
Body weight (kg)	65.7	63.9
	12.8	12.3
Body height (cm)	169.9	169.1
	9.4	9.3
Duration of isoflurane (min)	154.2	156.7
	56.6	26.8
Time intubation to extubation (min)	175.9	187.7
	56.2	24.8
Loading concn (vol %)	1.74	2.20
	0.16	0.11
Maintenance concn† (vol %)	1.24	1.57
	0.08	0.05

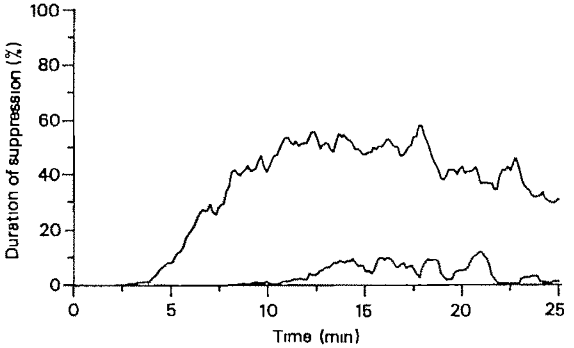

FIG. 1. Development of periods of burst suppression during the loading period (0–15 min) of isoflurane administration. The duration of the suppression is expressed as percentage of epoch size (8.192 s). The upper curve represents the group treated with 1.5 MAC, the lower curve the group treated with 1.3 MAC.

RESULTS

The actual vaporizer settings (mean ± SD) were 1.74 ± 0.16 vol% and 2.20 ± 0.11 vol% for the induction period for the 1.3 and 1.5 MAC groups, respectively. These loading concentrations were followed by maintenance concentrations of 1.24 ± 0.08 vol% and 1.57 ± 0.05 vol%, respectively.

During the loading period burst suppression patterns were seen in all patients in the group receiving 1.5 MAC, and in five patients in the group receiving 1.3 MAC. On average the duration of the period of suppression was shorter for patients receiving 1.3 MAC. Expressing the period of suppression as a percentage of the epoch duration (8.192 s), figure 1 compares the development of burst suppression (group average) with the commencement of isoflurane administration. Although the highest alveolar concentrations were

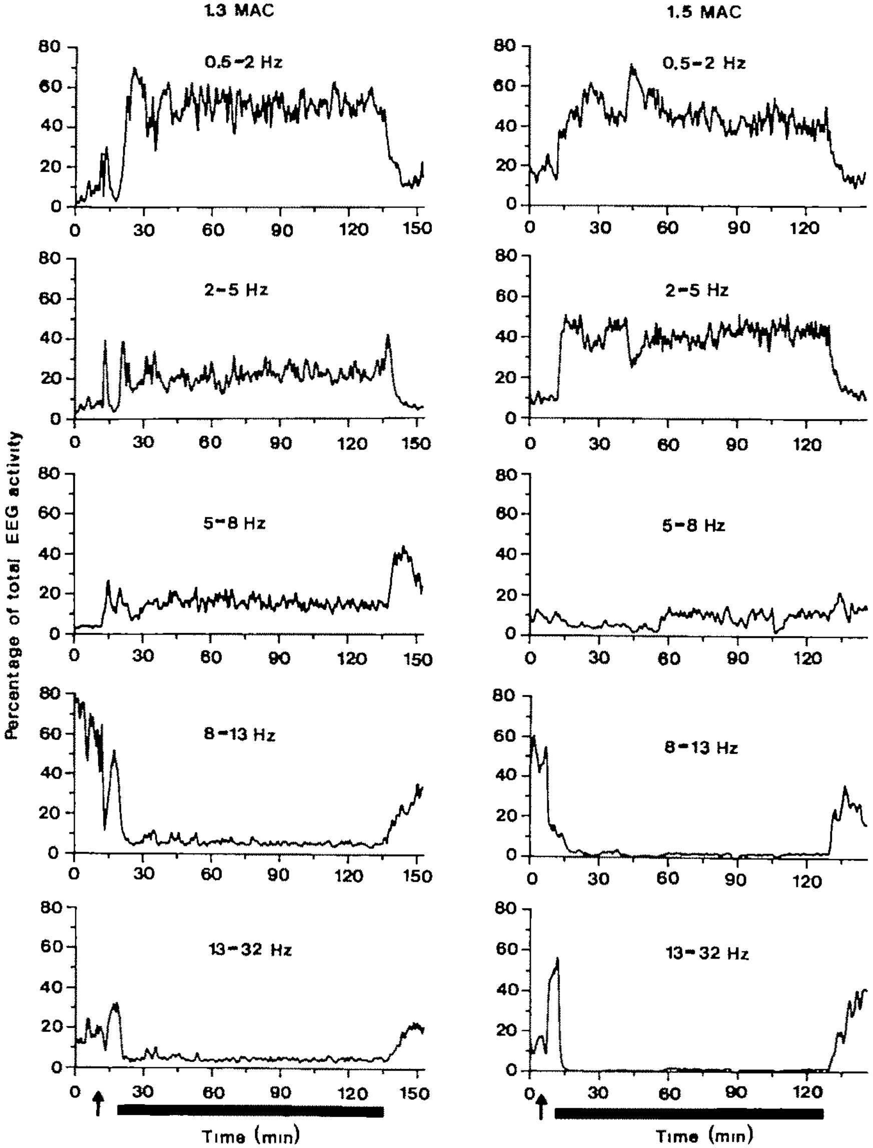

FIG. 2. Comparison of the time course of percentage of total EEG activity in the frequency bands indicated for two individuals of each group. ↑ = Induction of anaesthesia with thiopentone; —— = administration of isoflurane and nitrous oxide.

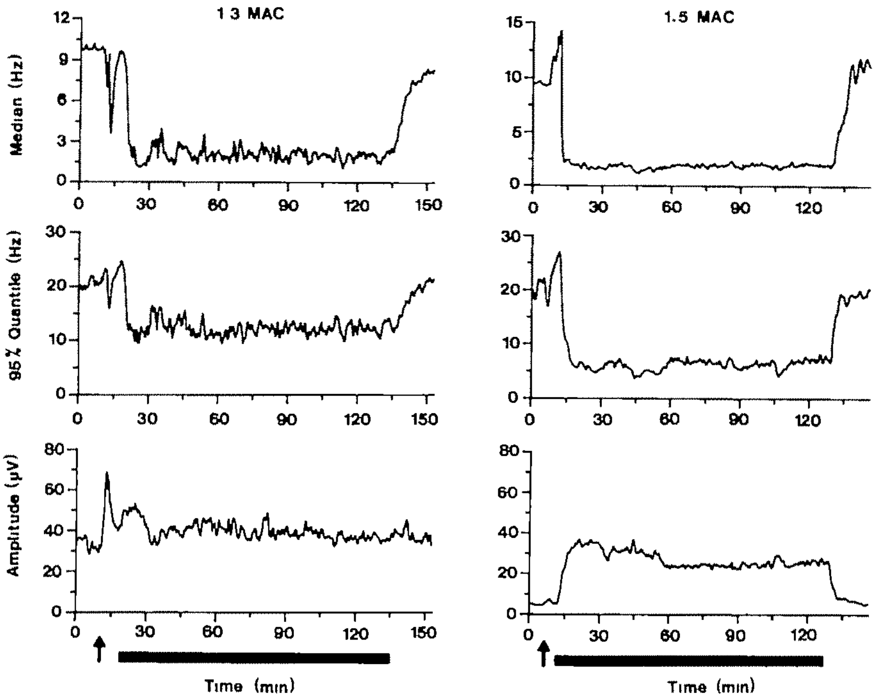

FIG. 3. Comparison of the time course of the EEG indices independent of the frequency band structure. Same individuals as in figure 2.

reached after terminating the loading period, the average duration of suppression did remain stable for a time.

Figure 2 gives two typical examples of the time course of activity, in the frequency bands indicated, for the group receiving 1.3 MAC (left hand side) and the group receiving 1.5 MAC. Both examples demonstrate that the theta band (5–8 Hz) changes little. It was only affected during induction and recovery, when activity moved from the high frequency bands (alpha and beta band) to the low frequency bands (< 5 Hz). The band 0.5–2 Hz can acquire up to 60% of total power. The median frequency, 95% quantile and mean amplitude, which are independent of the frequency band structure are depicted in figure 3. Both frequency measures, median and 95% quantile, exhibited consistently a decrease with increasing depth of anaesthesia; only at low concentrations—during induction and recovery—was activation of the high frequency bands, leading to transient increases in both measures of frequency, observed. Median frequency and 95% quantile were consistently lower in the patients receiving 1.5 MAC compared with 1.3 MAC.

TABLE II. *Distributions of various EEG variables during surgery (percentage of activity in the frequency bands 0.5–2 Hz, 2–5 Hz, 5–8 Hz, 8–13 Hz, 13–32Hz; median frequency (Hz), 95% quantile of EEG power spectrum (Hz) and mean amplitude (µV)) at the 5%, 25%, 50%, 75% and 95% quantiles. †Calculated according to formula (1); serves as a measure of the difference between two corresponding distributions*

	MAC	Quantile (%) 5	25	50	75	95	r†
Frequency band (Hz)							
0.5–2	1.3	21.5	31.0	41.1	57.8	80.9	0.23
	1.5	25.4	38.6	50.1	66.4	83.4	
2–5	1.3	13.1	22.4	29.3	38.1	47.6	0.20
	1.5	12.1	23.0	34.1	41.0	49.4	
5–8	1.3	2.4	5.9	12.0	15.1	20.0	0.28
	1.5	3.0	5.8	8.9	12.1	20.3	
8–13	1.3	1.6	4.1	8.1	11.5	20.1	0.64
	1.5	1.0	2.0	3.1	4.6	7.8	
13–32	1.3	2.0	3.8	5.4	7.0	11.1	0.69
	1.5	0.4	1.5	2.5	4.1	9.8	
Median (Hz)	1.3	1.1	1.8	2.5	3.2	4.0	0.24
	1.5	0.9	1.4	2.1	2.6	3.3	
95% Quantile (Hz)	1.3	5.4	10.0	12.3	14.0	17.5	0.84
	1.5	4.1	6.1	7.3	10.5	19.1	
Amplitude (µV)	1.3	6.3	29.3	45.6	68.1	81.8	0.43
	1.5	13.0	23.3	27.5	39.6	45.6	

TABLE III. *Distributions of various indices of EEG activity during surgery (percentage of activity in the frequency bands 0.5–2 Hz, 2–5 Hz, 5–8 Hz, 8–13 Hz, 13–32 Hz; median frequency (Hz), the 95% quantile of EEG power spectrum (Hz) and mean amplitude (μV)) at 5%, 25%, 50%, 75% and 95% quantiles. Distributions for the 1.3MAC and the 1.5MAC groups are combined. Comparison of distributions during different clinical periods: B = baseline EEG; A = surgical period; R = recovery phase. †Calculated according to formula (1), compare the distributions (B, A) and (A, R)*

		Quantile (%)					
		5	25	50	75	95	t†
Frequency band (Hz)							
0.5–2	B	3.4	5.9	9.3	14.0	20.4	1.25
	A	23.4	34.1	47.1	63.3	83.7	1.06
	R	4.5	11.0	14.8	20.0	27.5	
2–5	B	4.3	5.8	7.3	9.9	15.4	1.40
	A	12.5	22.8	32.1	40.0	49.4	1.30
	R	4.3	6.9	9.1	11.0	13.3	
5–8	B	3.4	4.6	5.8	7.9	13.9	0.48
	A	2.6	5.8	10.0	14.0	20.6	0.65
	R	5.1	13.8	20.4	27.6	52.6	
8–13	B	15.4	45.1	58.5	70.1	77.5	2.13
	A	1.1	2.5	3.9	8.1	16.4	1.69
	R	13.5	21.1	26.1	33.0	47.1	
13–32	B	10.4	14.8	19.6	26.3	42.6	1.30
	A	0.6	2.1	3.8	6.0	11.0	1.22
	R	10.2	19.4	26.6	37.6	47.4	
Median (Hz)	B	9.3	9.9	10.3	10.7	11.6	5.37
	A	1.0	1.6	2.2	2.8	3.9	1.86
	R	7.0	8.0	8.7	11.2	12.5	
95% Quantile (Hz)	B	17.8	20.0	21.5	23.2	26.5	1.62
	A	4.3	6.8	10.1	13.2	18.5	1.35
	R	16.5	18.7	20.4	23.0	25.8	
Amplitude (μV)	B	2.6	16.1	29.0	67.8	76.3	0.10
	A	6.6	24.4	34.8	46.1	78.5	0.48
	R	4.1	14.8	22.7	27.6	70.8	

For clinical purposes it would be advantageous to characterize the EEG changes by as few variables as possible. Given the selection of variables studied, and considering their suitability for discriminating between different depths of anaesthesia, we chose to characterize the distribution for the different EEG variables by the values at the 5, 25, 50, 75 and 95% quantiles. Denoting the 50% quantile of the distribution of the variable for 1.3 and 1.5 MAC by m_1 and m_2, and the difference between the 25 and 75% quantile by q_1 and q_2, we used the quantity t as a measure of the distance between the two distributions:

$$t = \frac{m_1 - m_2}{\sqrt{q_1^2 + q_2^2}} \qquad (1)$$

Table II compares the values (percentage of activity in the indicated frequency bands (%), median frequency (Hz), 95% quantile of EEG power spectrum (Hz) and mean amplitude (μV)) for the five selected quantiles for both groups. It is difficult to decide by statistical means whether two corresponding distributions are different or not. This is because one does not know to what extent two EEG epochs from which the variables are calculated can be regarded as independent events, thus affecting directly the degree of freedom of the distributions. Hence the t value cannot be used to test the hypothesis, but can be used to compare distances between distributions. From a clinical point of view, the large overlap between the distributions makes it virtually impossible to predict for a given EEG epoch, on the basis of the investigated variable, whether it belongs to the group treated with 1.3 or 1.5 MAC. Adopting this standpoint in table III, the distributions for 1.3 and 1.5 MAC are combined and compared with the distribution for the baseline EEG and the EEG recorded during the recovery period after having responded to command ("open your eyes") until cessation of EEG recording.

A graphical representation of the distribution of the variables is given in figure 4. It compares the baseline EEG (left hand side) with the intraoperative EEG (dashed) and the EEG during the recovery period. The most pronounced overlapping of the distribution during the recovery and intraoperative period is associated with the theta band (5–8 Hz), while the median frequency is the best discriminator between both periods. The mean time from cessation of isoflurane and nitrous oxide administration to response to commands was 13.4 ± 2.9 min for the group with 1.3 MAC and 30.0 ± 8.5 min for the group with 1.5 MAC. Trying to relate this time to the average values of the EEG variables 5 min before the end of surgery resulted in a non-significant relationship for each variable.

DISCUSSION

This study attempted to establish a quantitative basis for the EEG during anaesthesia with isoflurane at 1.3 and 1.5 MAC in 60% nitrous oxide and oxygen. The choice of these two concentrations was based on observations that, in most patients, clinical anaesthesia is achieved at alveolar concentration of 1.3 MAC or greater (Lowe and Ernst, 1981). The clinical impression that the quality of anaesthesia in both groups did

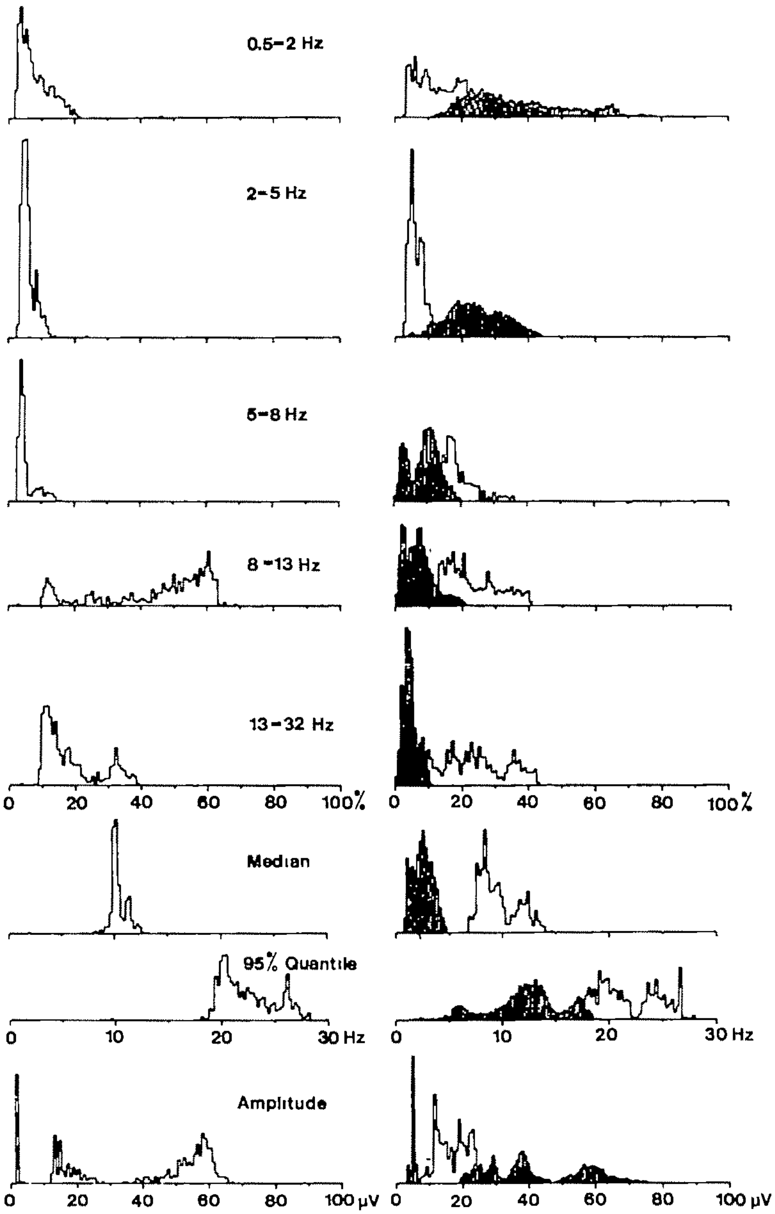

FIG. 4. Distribution of the investigated indices of EEG activity during various clinical periods. The distributions of both groups (1.3 MAC and 1.5 MAC) have been merged. The first five indices depict the distribution of the percentage of total EEG activity in the indicated frequency band. The left hand side depicts the distributions for the baseline EEG, the right hand side shows the corresponding distributions during surgery (shaded) and during recovery after having responded to command.

not differ to any apparent degree, might be reflected by the rather similar EEG behaviour observed in both groups during the surgical procedure. This might be an indication that the two isoflurane concentrations studied lie within the upper range of the isoflurane concentration–spectral EEG effect relationship. On the other hand one could argue that both concentrations lie too close to each other to cause significant differences. The vaporizer settings of isoflurane for 1.3 MAC and 1.5 MAC with 60% nitrous oxide differ, however, by more than 25%. This percentage increase in concentration leads to a marked prolongation in recovery at the end of surgery, and to quite different durations of burst suppression during the loading phase. As shown in this study, and as reported by others, burst suppression patterns can occur within the range of concentrations used in clinical practice (Eger, Stevens and Cromwell, 1971; Newberg, Milde and Michenfelder, 1983) and have immediate implications for the use of EEG monitoring devices based on spectral indices. Since burst suppression violates the assumptions (Schwilden and Stoeckel, 1985) underlying power spectrum analysis, and may cause misleading interpretations (Schwilden and Stoeckel, 1980; Levy, 1984), it is advisable to detect evidence of burst suppression before undertaking power spectrum analysis. The recognition of these patterns before spectral analysis may give relevant clinical information. In our experience, the presence of burst suppression indicates a depth of anaesthesia which is greater than that necessary to ensure unconsciousness and to prevent recall and awareness. On the other hand, it indicates that cerebral metabolism is decreased (Newberg, Milde and Michenfelder, 1983)—a feature which may, under certain circumstances, be regarded as a desirable therapeutic aim associated with anaesthesia.

Among the spectral variables studied, the median frequency showed the greatest degree of discrimination between the intraoperative period and the recovery phase. The spread of its distribution during the intraoperative period had an upper limit of about 5 Hz, and comparison of this distribution with that obtained once the patient had responded to command led to the conclusion that awareness recurs at the transition from median values less than 5 Hz to median values greater than 5 Hz. This is in agreement with earlier observations made with other drugs (Schwilden and Stoeckel, 1980; Schwilden, Schüttler and Stoeckel, 1985). Other authors have recommended the so-called "edge frequency" (Rampil et al., 1980) as a correlate of the depth of anaesthesia. However, as yet, its precise definition has not been published. Hudson and colleagues 1983), therefore, used the 95% quantile of the power spectrum distribution instead of the edge frequency. The problems with this index are that it is highly dependent on minor activities in the high frequency bands and reflects poorly the centre of the power spectrum distribution and the activities in the low frequency bands.

Some EEG monitoring devices neglect or attenuate the activities in the low frequency range (0.5–2 Hz) because most movement artefacts induce artificial low frequency activity. In the light of the finding that this band may contain up to 60% of total activity during anaesthesia, it could be disadvantageous to omit this band.

Although it is evident that a complex and, in general, multimodal distribution like an EEG power spectrum cannot be described fully by one index (Levy, 1984), it seems to be reasonable, on the basis of the results presented, to characterize the gross shifts of EEG frequency associated with anaesthesia by the median of the power spectrum.

We conclude that EEG devices designed to monitor trends of spectral correlates of depth of anaesthesia should allow low filter settings down to 0.5 Hz, depict some frequency measure, preferably the median EEG frequency, and be able to detect burst suppression, which may be characterized by the duration of the period of suppression either in absolute time or in time relative to the duration of the processed EEG epoch. The advantage of such a device in clinical practice is indicated by the results of this study. In order to minimize time to recovery, one would choose isoflurane concentrations as low as possible. Too low concentrations, however, risk too light a plane of anaesthesia. Median frequency values greater than 6 Hz can indicate awareness, as shown in figure 4 and table III. Especially when using neuromuscular blocking agents, this might be the only indication of awareness. Thus, titrating isoflurane concentrations so that median frequency values remain below those values associated with awareness, could help prevent too light planes of anaesthesia. The recognition of burst suppression, on the other hand, may help either to avoid too deep levels of anaesthesia or to confirm that brain metabolism is decreased.

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COMPARISON OF MIDAZOLAM BY MOUTH AND DIAZEPAM I.V. IN OUTPATIENT ORAL SURGERY

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SUMMARY

In a randomized double-blind, parallel groups study, 40 patients undergoing surgical removal of impacted 3rd molar teeth received either midazolam 15 mg orally followed at 35 min by i.v. saline, or oral placebo followed at 35 min by i.v. diazepam 10 mg (Diazemuls). Rapid onset of sedation was seen after midazolam, while the pattern and duration of postoperative sedation, as measured by standard psychometric tests, indicated slower recovery after midazolam than after diazepam. Ratings by the surgeon indicated superior anxiolysis following midazolam and significantly more patients expressed a preference for oral midazolam sedation. Significant, comparable anterograde amnesia was seen with both treatments. No significant cardiovascular complications occurred with either treatment. The findings indicate that rapidly acting oral benzodiazepines such as midazolam provide safe, effect alternatives to i.v. diazepam for conscious sedation in outpatients undergoing minor surgical procedures.

Many surgical procedures are now performed, on a day-stay basis, in hospitals and dentists' surgeries under regional anaesthesia supplemented with sedation (Philip, 1985). Although i.v. benzodiazepine sedation has become a well established technique for such procedures (Philip, 1985), there are a number of hazards associated with i.v. regimens (Editorial, 1976). The increasing availability of new benzodiazepines which are rapidly absorbed after oral administration, and which have a relatively short duration of action, raises the possibility that oral administration may be a suitable alternative to an i.v. technique. Temazepam by mouth has been shown to be comparable to i.v. diazepam for both gastroscopy (Douglas et al., 1980) and oral surgery (O'Boyle, Harris and Barry, 1986).

Midazolam is a potent water-soluble benzodiazepine which is characterized by a very rapid onset of action (Dundee et al., 1980; Pieri et al., 1981). It has a short duration of action because the methyl group on the imidazole ring allows rapid oxidation by the liver (Gereke, 1983). Of particular interest in the present context was the finding that, at identical plasma concentrations, the oral dose induced more marked effects than the i.v. dose (Crevoiser et al., 1983). This appeared to be attributable to the active alpha-hydroxy metabolite, which has a short half-life and was found in greater plasma concentrations in the first 2 h after the oral than after the i.v. administration of the parent midazolam (Crevoiser et al., 1983; Ziegler et al., 1983).

In a pilot study of 10 dental outpatients, we found that midazolam 10 mg by mouth resulted in significant anxiolysis at 30 min and good operating conditions in all patients (unpublished data). While patient satisfaction with midazolam was high, it was felt that better amnesia might be obtained with a 15-mg dose. The present study was designed as a placebo-controlled assessment of the rapidity of onset and degree of anxiolytic activity produced by the oral administration of midazolam in outpatients undergoing removal of 3rd molar teeth. The design, which has been used previously to assess the efficacy of temazepam by

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mouth (O'Boyle, Harris and Barry, 1986), further allowed comparison of conscious sedation obtained after midazolam given orally with that seen after a standard i.v. dose of diazepam.

PATIENTS AND METHODS

Forty fit adult outpatients who were judged to require sedation for the removal of impacted 3rd molar teeth gave informed written consent to the study, which was approved by the hospital ethics committee. Patients were excluded if they had any clinically significant deviation from normal on medical examination, a history of asthma, allergic conditions or drug hypersensitivity, or if they were being treated with a benzodiazepine.

Procedure

Patients reported to the hospital 1 h before their scheduled dental treatment, a maximum of three patients being studied during one session. The design of the study and the schedule of assessments are shown in figure 1. The study was blind to the surgeon and the psychologist, but the anaesthetist, who was not involved in any of the assessments, was aware of the regimen received by each patient. Neither the surgeon nor the psychologist was present during the administration of any medication. Patients were allocated to treatment conditions by means of a random number table. Group I ($n = 20$) received midazolam 15 mg (Hypnovel, Roche Products Ltd) by mouth 35 min before saline 2 ml i.v., given 5 min before the start of the procedure. Group II ($n = 20$) received matching placebo capsules by mouth, then diazepam 10 mg (Diazemuls, Kabi-Vitrum) i.v. 35 min later. This was injected at a rate of 2.5 mg per 30 s through a "Butterfly" cannula inserted to a large vein in the antecubital fossa. After the i.v. injection the appropriate nerve block was performed with 2% lignocaine containing adrenaline 1:80000. A standard surgical procedure was adopted which consisted of the removal of impacted 3rd molars under inferior dental nerve blockade. Cardiovascular function was monitored before, at specific times during (local analgesia, incision, drilling, extraction, suturing) and after surgery. Verbal contact was maintained with the patients throughout the surgical procedure. After the operation patients were taken to the recovery ward where psychometric tests were administered. All patients were capable of being discharged in the company of a responsible adult at 120 min. They were provided with routine analgesic medication and instructed on the relevant precautions in the presence of the accompanying adult.

The next week patients returned to the clinic where memory was tested and questionnaires detailing postoperative state and satisfaction with sedation were administered.

Assessments

Anxiety. State anxiety was assessed by means of the state scale of the Speilberger State Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch and Lushene, 1970), which has been shown to be sensitive to the anxiolytic effects of benzo-

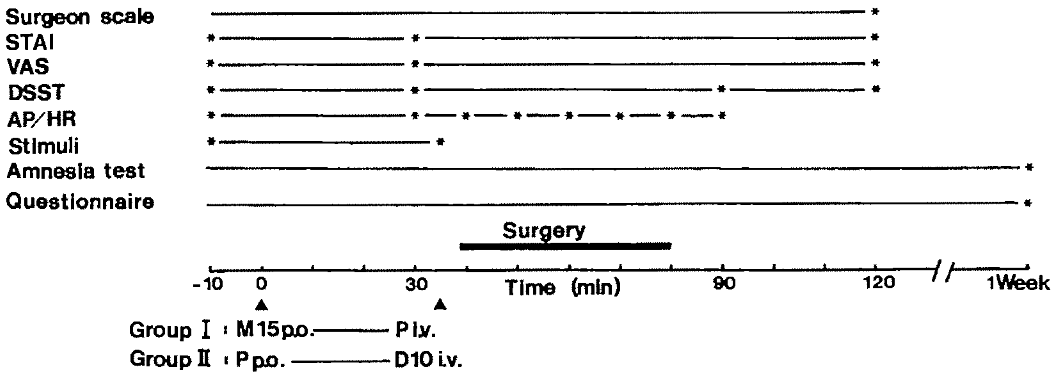

FIG. 1. Study design. Group I received midazolam 15 mg by mouth (M15p.o.) followed at 35 min by saline i.v. (Pi.v.). Group II received placebo by mouth (Pp.o.) followed at 35 min by diazepam 10 mg i.v. (D10i.v.). *Denotes the timing of the various assessments. STAI = State Anxiety Scale; VAS = Visual Analogue Scales; DSST = Digit Symbol Substitution Test; AP/HR = Arterial pressure/Heart rate; Stimuli = visual memory stimuli.

diazepines in the context of dental surgery (O'Boyle, Harris and Barry, 1986). Visual analogue scales (VAS) (100-mm) measuring anxiety and tension were also used. Trait anxiety about dental procedures was assessed by means of the Corah Dental Anxiety Scale (Corah, 1963).

Psychomotor function. The onset of impairment in psychomotor function and subsequent recovery of normal function were measured by means of the digit symbol substitution test (DSST) which was administered in the standard manner (Wechsler, 1955). This test has previously been found to be sensitive to the effects of benzodiazepines and to be suitable for administration in the outpatient surgical setting (O'Boyle et al., 1983; O'Boyle, Harris and Barry, 1986). Visual analogue scales measuring drowsiness, mental slowness and clumsiness were also completed. All operations and test procedures were conducted in the afternoon to control for the possible influence of circadian rhythms on psychomotor performance.

Amnesia. Amnesia was assessed by means of two complementary techniques: a visual memory test and a subjective questionnaire. Before the administration of either midazolam or placebo, patients were shown six photographs: three of commonplace objects and three of objects relevant to dentistry. A second set of stimulus photographs, similar to the first, was shown when patients were lying on the operating table, immediately before the administration of the local anaesthetic drug (that is, 5 min after the i.v. injection). Photographs were shown sequentially, at the rate of one every 5 s and patients were required to name the objects represented in order to ensure that the stimuli were registered. The timing of the second set of stimuli was such that it was shown to group I 40 min after the oral administration of the midazolam and to group II 5 min after the i.v. diazepam. This was done in order to permit adequate absorption of the midazolam before the memory stimuli were presented. The recall part of the test took place 1 week later in the same operating theatre. Patients were given a set of 24 photographs consisting of the 12 which had been shown the previous week and 12 which had not been shown (buffers). Recognition memory was tested by asking patients to identify those photographs which they had seen. Recognition of photographs previously seen in the absense of any medication provided a measure of normal amnesia against which drug-induced amnesia was assessed.

Patients also rated their memory for specific events (taking tablets, i.v. injection, local analgesia, drilling, extraction, performance of tests and going home) on a three-point scale: "perfectly", "vaguely" or "not at all".

Cardiovascular function. Systolic (SAP) and diastolic (DAP) arterial pressures and heart rate (HR) were monitored (Dinamap 847 automatic monitor).

Surgeon's ratings. The surgeon rated anxiety, co-operation, relaxation, ease of access, degree of swallowing and ptosis on a series of 100-mm visual analogue scales (O'Boyle, Harris and Barry, 1986). The general impression of the sedation ("good", "satisfactory" or "poor") was also rated by the surgeon.

Patient's ratings. Patients' satisfaction with sedation ("good", "satisfactory" or "poor"), opinion of the operation ("better" or "worse" than expected) and future sedation preference ("no sedation", "this method" or "other method") were recorded by questionnaire during the return visit. A questionnaire designed to measure fatigue, confusion, nausea, pain and global normality during the evening after the operation was also completed at this time.

Statistical analysis

Data from the DSST, STAI and patient VAS were converted to change scores by subtracting scores obtained at 30 and 120 min from control scores. Differences between the two treatment groups on the DSST, STAI, SAP, DAP, HR, patient and surgeon VAS, and the visual memory test were assessed by analysis of variance. Global ratings by patient and surgeon, and the data from the follow-up questionnaire, were compared using the Chi-square test. The design of the study was such that comparisons at 30 min were between oral midazolam and placebo, and subsequent comparisons were between oral midazolam and i.v. diazepam (fig. 1).

RESULTS

There were relatively more males than females in group II (placebo/diazepam) and this group tended to be taller and heavier than group I, although the differences were not significant (table I). Before sedation the two groups were comparable on the DSST and STAI, but there was a strong tendency for group I to rate their everyday fear of dentistry as higher on the Corah scale. This group showed significantly ($P < 0.001$) more

TABLE I. *Patient characteristics (means ± SD). ***P < 0.001 for ANOVA pairwise comparison between groups*

	Midazolam by mouth +placebo i.v.	Placebo by mouth +diazepam i.v.
Age (yr)	24.4±4.4	23.2±4.0
Weight (kg)	56.8±7.6	60.6±7.7
Height (cm)	166.9±6.3	171.4±7.8
Corah Anxiety Score	11.4±3.5	9.4±2.7
Baseline Anxiety (STAI)	47.9±12.3	43.3±10.1
Baseline Anxiety (VAS) (mm)	73.3±22.6	43.9±22.8***
Sex (M/F)	5/15	9/11

TABLE II. *Mean visual analogue scale scores (±SD) for the surgeon's assessment of the two treatment groups. **P < 0.01; *P < 0.05 for ANOVA pairwise between-group comparisons*

Scale	Midazolam by mouth +placebo (mm)	Placebo by mouth +diazepam i.v. (mm)
Anxiety	42.6±27.0	66.4±25.7**
Co-operation	79.9±12.4	78.1±16.7
Relaxation	50.2±20.0	33.0±20.2*
Ease of access	74.6±18.3	77.2±16.3
Degree of swallowing	33.0±29.3	32.2±22.3
Degree of ptosis	60.9±15.1	51.9±15.4

anxiety on the VAS. Two patients in the diazepam group and one patient in the midazolam group failed to return for follow-up assessment.

Surgeon's ratings

The surgeon's VAS ratings indicated that patients who had received oral midazolam (group I) were significantly less anxious ($P < 0.01$) and were more relaxed ($P < 0.05$), during the procedure than those who had received diazepam i.v. (table II). Global ratings indicated that sedation was good or satisfactory in the majority of patients (18) in both groups. Sedation with midazolam was rated as poor in two female patients, one of whom was very anxious about dentistry and was anxious throughout the procedure. Subsequently, she rated her sedation as good, and indicated a preference for midazolam. The second patient underwent a difficult extraction of a lower 3rd molar, which required considerable bone removal and sectioning of the tooth. This patient showed distress during drilling; subsequently, she rated

TABLE III. *Patients' responses to the follow-up questionnaire administered 1 week after the operation. Figures are percentages with the number of patients in brackets. Three patients failed to return for assessment. *P < 0.05 for Chi-square comparisons between the treatment groups*

	Oral midazolam (n = 19)				I.v. diazepam (n = 18)			
Rating	Not at all	Somewhat	Moderately so	Very much so	Not at all	Somewhat	Moderately so	Very much so
Tired	21.1(4)	26.3(5)	31.6(6)	21.1(4)	27.8(5)	22.2(4)	16.7(3)	33.3(6)
Confused	63.2(12)	36.8(7)	0.0	0.0	77.8(14)	11.1(2)	5.6(1)	5.6(1)
Sick	89.5(17)	5.3(1)	0.0	5.3(1)	72.2(13)	16.7(3)	5.6(1)	5.6(1)
Pain	10.5(2)	31.6(6)	21.1(4)	36.8(7)	33.3(6)	5.6(1)	38.9(7)	22.2(4)
Normal	15.8(3)	26.3(5)	26.3(5)	31.6(6)	33.3(6)	11.1(2)	27.8(5)	27.8(5)
	Better	Worse	No opinion		Better	Worse	No opinion	
Opinion of operation	57.9(11)	26.4(5)	15.7(3)		50.0(9)	44.4(8)	5.6(1)	
	Poor	Satisfactory	Good		Poor	Satisfactory	Good	
Satisfaction	10.5(2)	31.6(6)	57.9(11)		33.3(6)	33.6	33.6	
	This method	Other method			This method	Other method		
Future preference	89.5(17)	10.5(2)			61.1(11)	38.9(7)*		

TABLE IV. *Mean(+SD) change from baseline in anxiety on the STAI and VAS at 30 (preoperative) and 120 (postoperative) min after oral administration. Note that the 30-min comparison is between midazolam and placebo.* *$P < 0.05$; ***$P < 0.01$ *for ANOVA pairwise between groups comparisons*

Assessment	Time (min)	Midazolam by mouth +placebo i.v.	Placebo by mouth +diazepam i.v.
STAI	30	−7.3+10.0	−4.7+8.1
	120	−14.4+13.0	−10.3+11.0
VAS	30	−17.9+22.5*	−4.9+11.8
	120	−50.4+28.0***	−17.2+22.6

her sedation as poor and indicated a preference for some other type of sedation. Sedation after i.v. diazepam was poor in one female and one male patient. The female patient reacted with intense distress when her mouth was touched at the beginning of, and throughout, the operation, despite having indicated little anxiety and fear of dentistry. Subsequently, she rated the sedation as poor and the operation as worse than expected. In the second patient verbal protest and movement were seen on administration of the local anaesthetic. While this patient rated the operation as worse than expected, he rated his sedation as good.

Patient ratings

Patients in the midazolam group showed greater satisfaction with their sedation than those in the diazepam group (table III). Of the 19 patients who received midazolam by mouth and who returned at 1 week, 17 (89.5%) indicated a preference for "this type of sedation", compared with 11 of the 18 (61.1%) who received i.v. diazepam ($P < 0.05$). Six patients rated diazepam sedation as poor compared with two in the midazolam group. None of the questions about the state of the patients on the evening after operation showed significant between-group differences.

Patient anxiety

The two groups did not differ significantly on the STAI during the control period. The change from baseline after midazolam was comparable to that seen after placebo, at 30 min and at 120 min after surgery (table IV). On the VAS rating, the midazolam group was significantly more anxious than the diazepam group ($P < 0.001$) before medication (table I). The change in VAS rating from baseline 30 min after midazolam was significantly greater than that after placebo ($P < 0.05$), indicating a moderate anxiolytic effect at this time (table IV).

Psychomotor performance

Compared with placebo, scores on the DSST test showed a highly significant ($P < 0.001$) deterioration at 30 min after midazolam, indicating rapid onset of drug effect (table V). This decrease in performance was accompanied by increased subjective mental slowness ($P < 0.05$): 120 min after surgery, patients in the midazolam group rated themselves as more drowsy ($P < 0.05$) than those in the diazepam group. There was also a tendency for DSST performance to decrease after midazolam at this time.

Amnesia

Visual memory test. As expected, memory for photographs seen before medication, an index of normal amnesia, was comparable in the two groups (fig. 2). On average, patients in group I remembered 5.53 stimuli out of a possible 6, while patients in group II remembered 5.73. Marked amnesia was seen in both groups for photographs which had been shown after sedation. On average, only 1.70 of the photographs seen after oral midazolam were recognized (control 5.53) ($P < 0.001$). In the i.v. diazepam group, the memory score decreased from a control figure of 5.73 to 0.91 ($P < 0.001$). The degree of amnesia for the photographs seen after treatment did not differ between the two groups and recognition of dental and neutral photographs was equally affected.

Memory questionnaire. When questioned at 1 week, all patients recalled perfectly taking tablets before operation (fig. 3). All patients who received oral placebo recalled the i.v. injection, but less than half (47.4%) of those who had been given midazolam did so perfectly ($P < 0.001$). There

TABLE V. *Objective and subjective sedative effects of the treatments. Results are expressed as mean (SD) changes from baseline. Negative values represent decreased performance and alertness. The 30-min comparison is between oral midazolam and placebo.* *$P < 0.05$; ***$P < 0.001$ *for ANOVA pairwise between-group comparisons*

Test	Treatment	Time since oral medication (min)		
		30	90	120
DSST (Score/90 s)	Midazolam by mouth	−10.9±12.6***	−6.8±6.4	−6.2±8.0
	Diazepam i.v.	+3.5±6.8	−3.2±11.2	−0.7±11.5
Alert (mm)	Midazolam by mouth	−20.6±22.9		−25.5±25.3*
	Diazepam i.v.	−9.6±20.1		−6.9±26.1
Quick-witted (mm)	Midazolam by mouth	−13.5±23.2*		−17.7±33.5
	Diazepam i.v.	+2.7±24.8		−1.7±22.5

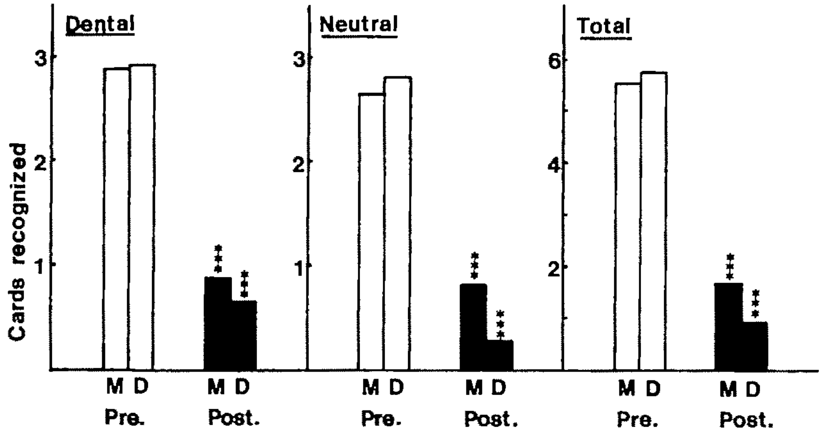

FIG. 2. Visual memory test: mean number of cards correctly recognized at 1 week. Pre. = cards previously seen before medication. Post. = cards previously seen 5 min after i.v. diazepam 10 mg (D) or 40 min after oral midazolam 15 mg (M). ***$P < 0.001$ for pre.–post. comparisons within treatments. No significant differences were found between treatments.

was a strong trend for patients who had received oral midazolam (40 min previously) to show greater amnesia for the local anaesthetic injection than those who had received i.v. diazepam (5 min previously). Oral midazolam tended also to produce greater amnesia for drilling and tooth extraction, but the difference was not significant. The duration of midazolam-induced amnesia tended to be greater than that of diazepam, as reflected in a trend for more patients in the midazolam group to show amnesia for the postoperative tests.

Cardiovascular function

Control data were analysed by a series of 2(treatments: midazolam/placebo) × 20(subjects) × 2(observation periods: before medication/ 30 min after medication) analyses of variance (ANOVAS) with repeated measures on the observations factor. A highly significant treatments by observations interaction was found for SBP ($P < 0.001$) (table VI). Average SBP increased from a control figure of 114.6 mm Hg to 121.9 mm Hg before the i.v. injection in the placebo group, but decreased from 123 mm Hg to

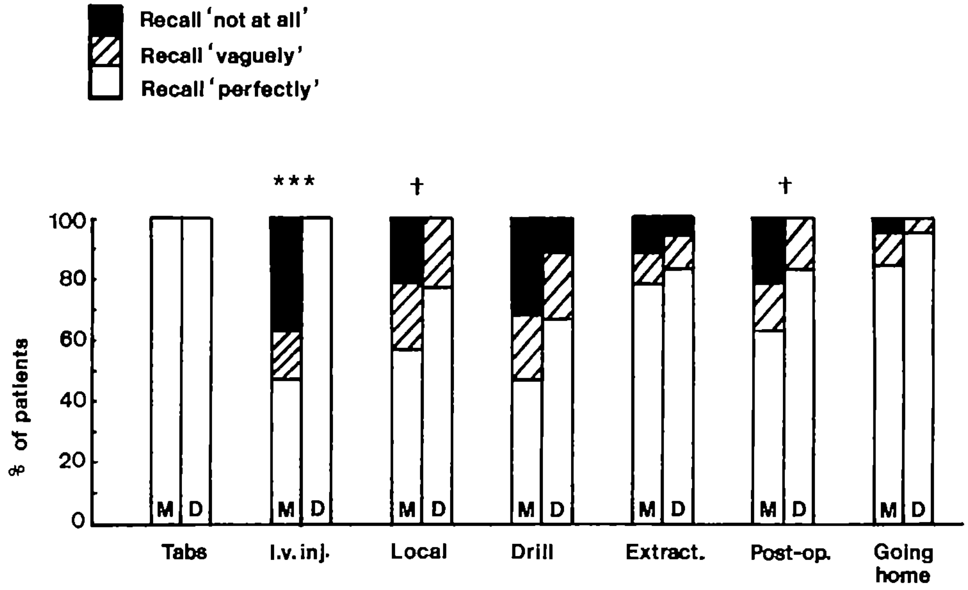

FIG. 3. Patients' recall of specific operative events for the midazolam+placebo (M) and the placebo+diazepam (D) conditions. ***$P < 0.001$ for Chi-square comparison between midazolam placebo. †$P < 0.10$ trend for comparison between oral midazolam and i.v. diazepam.

TABLE VI. *Mean values (SD) for systolic (SAP) and diastolic (DAP) arterial pressure and heart rate (HR) for the two treatment groups. Pre-med. = before either midazolam 15 mg by mouth or placebo; Pre-i.v. = before i.v. placebo or diazepam 10 mg; Post-op. = 10 min after operation.* †$P < 0.001$ *treatments by observations ANOVA interaction for SAP for pre-medication and pre-i.v. observations.* ‡*Significant intraoperative ANOVA observations effect for SAP* ($P < 0.001$)*, DAP* ($P < 0.01$) *and HR* ($P < 0.001$)*, reflecting progressive increases in values*

	Procedure							
	Pre-med.	Pre-i.v.	Local analgesia	Incision	Drilling	Extraction	Suturing	Post-op.
HR (beat min^{-1})‡								
Midazolam	77.4	77.1	78.0	91.9	92.7	92.1	87.9	84.0
	(12.3)	(10.1)	(12.5)	(11.5)	(10.8)	(11.3)	(12.7)	(12.9)
Diazepam	67.6	69.4	77.2	86.6	88.5	88.0	82.1	78.8
	(11.2)	(12.2)	(11.3)	(15.2)	(19.0)	(17.3)	14.7	(13.4)
SAP (mm Hg)†‡								
Midazolam	123.0	115.6	119.0	120.1	124.4	122.6	122.4	117.9
	(10.7)	(10.6)	(11.7)	(8.6)	(12.0)	(13.1)	(11.4)	(12.1)
Diazepam	114.6	121.9	116.1	124.3	127.1	127.6	126.0	123.1
	(13.1)	(13.5)	(12.5)	(17.0)	(18.3)	(19.2)	(14.9)	(18.4)
DAP (mm Hg)‡								
Midazolam	70.0	64.6	66.5	61.6	67.5	67.5	69.6	63.2
	(8.4)	(8.0)	(8.0)	(8.9)	(10.8)	(8.4)	(13.0)	(8.1)
Diazepam	66.7	68.5	65.2	63.4	70.3	70.3	68.2	66.2
	(10.7)	(11.9)	(10.3)	(9.9)	(13.4)	(20.9)	(19.2)	(14.8)

115.6 mm Hg after oral midazolam. No significant differences were found between the treatment groups during surgery. Significant observations effects were found for SBP ($P < 0.001$), DBP ($P < 0.01$) and HR ($P < 0.001$), reflecting progressive increases in cardiovascular activation as the operation progressed, regardless of the type of sedation.

DISCUSSION

The results indicate that 15 mg of midazolam by mouth is superior, in some respects, to a 10-mg dose of i.v. diazepam for conscious sedation in association with outpatient oral surgery. It must be noted that the dose of i.v. diazepam used in this study was titrated to a maximum of only 10 mg to allow comparison with previous findings for temazepam (O'Boyle, Harris and Barry, 1986). The onset of action of midazolam was rapid, with significant impairment in the DSST and VAS, as well as significant amnesia, occurring as early as 30 min after administration. The surgeon's ratings of patient relaxation and anxiety indicated better sedation in the midazolam group despite the fact that this group was more anxious before the procedure, and had greater general fear of dentistry as measured on the Corah scale.

Recovery of normal function after i.v. midazolam is generally more rapid than that seen after i.v. diazepam. For example, after midazolam 5 mg, motor performance recovered at 34 min and subjects were fully awake and walking after 73 min (Dundee et al., 1980; Gamble et al., 1981). With larger doses, sedative effects can be prolonged. McClure, Brown and Wildsmith (1983) have shown that 50% of patients who received 0.19 mg kg^{-1} for spinal anaesthesia were still asleep at 3 h. In the present study recovery of normal function was more rapid after i.v. diazepam 10 mg than after oral midazolam 15 mg. The half-life of midazolam, following oral administration, is of the order of 2 h (Amrein et al., 1983) and that of its active metabolite alpha-hydroxy midazolam is about 1 h (Heizmann, Eckert and Ziegler, 1983). However, there is not necessarily a direct relationship between plasma concentrations of a benzodiazepine and residual sedation. Patients in the present study were tested for 120 min after drug administration so it is impossible to say when complete recovery of function occurred. There was a trend for patients who received diazepam to report that they had felt more confused during the evening of their operation, an effect possibly attributable to enterohepatic recirculation (Baird and Hailey, 1972).

The specific anxiolytic activity of midazolam was not as marked as that seen previously with temazepam under similar test conditions (O'Boyle, Harris and Barry, 1986). Although marked sedative activity was seen 30 min after midazolam in the present study, this was not accompanied by marked subjective anxiolysis. With temazepam, sedation was accompanied by marked anxiolysis. Animal studies, using the anti-conflict test as an anxiety model, have shown that the specific anxiolytic actions of midazolam are not as marked as those of diazepam (Pieri et al., 1981). The distinction between the anxiolytic and sedative properties of drugs used as supplementary medication for procedures performed under regional anaesthesia, is of increasing importance given the development of new non-sedative anxiolytics (Poggioli, Bonnet and Von Frenckell, 1985).

Significant cardiovascular complications did not occur in either treatment group. Midazolam reduced preoperative SAP, which increased in the placebo group as the start of the operation approached. Cardiovascular responses to operative events were not prevented by sedation in either treatment group. This is in agreement with previous findings with temazepam (O'Boyle, Harris and Barry, 1986) and diazepam (Goldstein et al., 1982).

Amnesia is an important feature of conscious sedation (Kanto, 1981) and is usually more profound after i.v. benzodiazepines (Pandit, Dundee and Keilty, 1971). The effect of diazepam on memory consolidation is blocked by the specific benzodiazepine antagonist Ro 15-1788, indicating that the benzodiazepine receptor is the site of action (O'Boyle et al., 1983). Generally, i.v. midazolam has been found to produce greater amnesia than i.v. diazepam (Berggren et al., 1983; Magni et al., 1983; Dixon et al., 1984). In this study, the results of the objective test revealed a similar degree of marked amnesia with both drugs. Patient recall of actual events also reflected rapid onset of amnesia with midazolam. At 30 min over half of the patients who had received midazolam had some degree of amnesia for the i.v. injection. The degree of amnesia tended to be greater than that seen after i.v. diazepam and to be of longer duration. Interestingly, more marked amnesia was seen for artificial stimuli than for actual events.

Oral administration of a benzodiazepine with a short half-life and a rapid onset of action is proving increasingly useful in a number of settings (Male and Johnson, 1984; O'Boyle, Harris and Barry, 1986). The present findings indicate that midazolam by mouth provides relatively rapid sedation and amnesia of a degree sufficient for a highly stressful surgical procedure. Despite its short half-life, patients may need some time to recover normal function following the surgical procedure.

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EFFECT OF NASOTRACHEAL INTUBATION ON NASAL MUCOCILIARY CLEARANCE

S. ELWANY AND A. MEKHAMER

SUMMARY

Forty patients were studied to investigate the effect of nasotracheal intubation on nasal mucociliary clearance measured with the radio-paque disc method under standard conditions. Postoperative mucociliary slowing on the intubated side was observed in 65% of patients. Difficult or prolonged intubation increased the incidence of mucociliary stasis. Age, sex, smoking history, tube size and the use of lubricants had no effect. Postoperative slowing of the clearance rate was most probably the result of mechanical trauma to the superficial epithelial layers, and recovery of function was reasonably rapid with conservative management.

The hazards of tracheal intubation have been well documented since the introduction of the technique over a century ago. Although the risk of major injury to the airway has been of concern to the otorhinolaryngologist, most discussion has centred around laryngotracheal damage. Interestingly, the effect of intubation on the nasal respiratory mucosa has received little attention despite the importance of the nasal mucociliary transport system. This study was undertaken to investigate the effect of nasotracheal intubation on nasal mucociliary clearance.

PATIENTS AND METHODS

Ethical approval was obtained from the local Director of Medical Education and Research, and all patients gave written, informed consent.

Patients

Forty patients (16 female; mean age 36, range 15–48 yr) who were scheduled to undergo elective abdominal, gynaecological or limb operations, agreed to enter the study. Only patients for whom nasal intubation seemed more suitable were included, and more than 3 years was needed to collect the series.

A questionnaire on respiratory symptoms (Brille et al., 1972) was completed by each patient—and revealed no recent or chronic nasal dysfunction. Seventeen patients had never smoked, and 23 were intermittent smokers with low average tobacco consumption (Puchelle et al., 1981). Patients with slow preoperative mucociliary clearance were excluded from the study. In order to exclude any possible effect of general anaesthesia on the clearance rate, all patients who had bilaterally slow clearance after surgery were also excluded.

Anaesthetic technique

Patients were premedicated with diazepam 0.2–0.6 mg kg^{-1}. Atropine and hyoscine were not used because of their possible effects on mucociliary clearance (Proctor and Andersen, 1982). Anaesthesia was induced with thiopentone 3–4 mg kg^{-1} i.v. After the administration of suxamethonium 1 mg kg^{-1} i.v., the trachea was intubated atraumatically. The size of the nasotracheal tube was determined by the anaesthetist. Anaesthesia was maintained with 1.5–2% halothane and 65% nitrous oxide in oxygen. In 20 patients, the tracheal tube was lubricated with a standard jelly without a bacteriostatic or local anaesthetic agent.

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Measurement of mucociliary clearance

Measurement of mucociliary clearance, in both sides of the nose, was performed before, and on the 3rd, 7th and 10th days after surgery. All measurements were made in the same room with a temperature of 20 ± 1.0 °C, and a relative humidity of 60 ± 8.0 %. The day-to-day reliability of the measurements was controlled by repeating the measurements exactly 24 h later. Duplicate measurements, 1 h apart, were performed in all patients in whom clearance was slow. The reliability of measurements taken 24 h apart and the validity of duplicate measurements in proving true slowing of mucociliary clearance have been demonstrated previously (Yergen et al., 1978; Puchelle et al., 1981).

Mucociliary clearance was measured using a radiographic method, the safety and validity of which have been described (Friedman et al., 1977; Yergen et al., 1978). Radiopaque Teflon discs, 1–2 mm in diameter, were used (Yergen et al., 1978). Two discs were dropped gently onto the superior surface of the inferior turbinate, 1 cm behind its anterior end, and a lateral radiograph taken. The discs were followed with a fluoroscopic image intensifier until they reached the posterior border of the vomer (or 45 min had elapsed) when another radiograph was taken (fig. 1). The safety of using image intensifiers is well established and not more than eight radiographs were needed in any single patient.

The transport time (*T*) was determined by measuring the time between the placement of the discs and the moment when they reached the posterior border of the vomer. The corresponding distance (*d*) was also measured on the film. To calculate the true transport velocity, the magnification correction factor must be determined (Meschan, 1975). This was achieved by fixing a radiopaque tape on the patient's cheek and measuring its actual length (*L*) as well as its length on the film (*l*). To ensure accuracy of the measurements, all radiographs were exposed with the patient in the erect position with the head fixed by a wall-mounted "cephalostat" and orientated with the Frankfort horizontal plane. The tube–cassette distance was 180 cm. With this arrange-

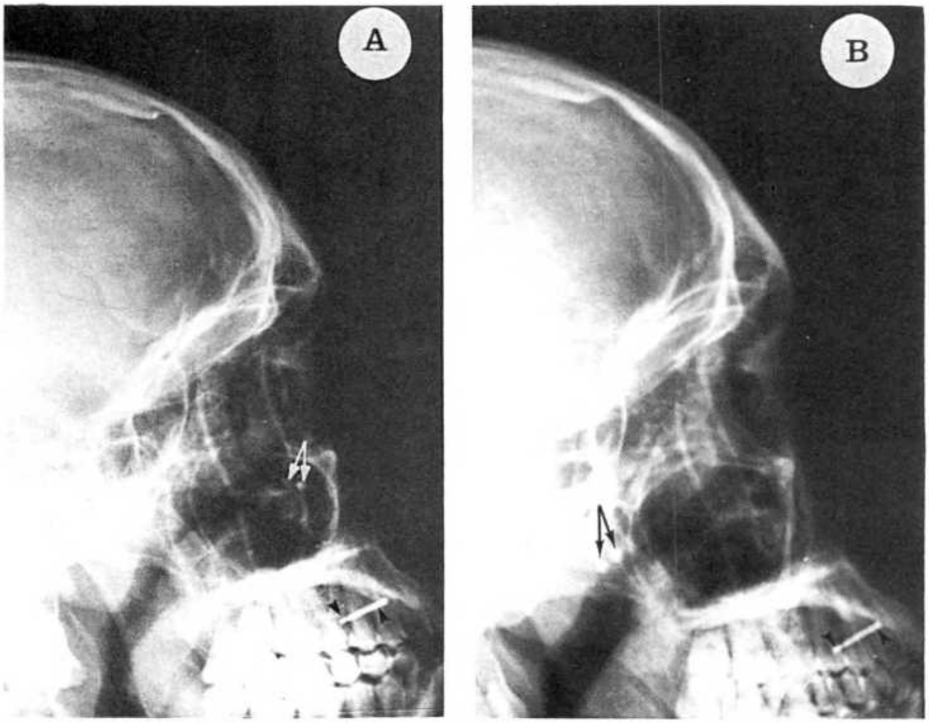

FIG. 1. Radiopaque disc method. Lateral radiograph of the skull showing the radiopaque discs (arrows) at the anterior end of the inferior turbinate (A) and opposite the posterior border of the vomer (B). A radiopaque tape (arrowheads) is fixed on the cheek for calculation of the magnification correction factor.

ment, the median plane was enlarged by 65%. Exposures were made at 100 kV and 50 mA.

The transport velocity (V) of the discs was determined after calculating the actual distance (D) moved by the particles using the following equations:

$$D = d \times L/l \,(\text{mm})$$

$$V = D/T \,(\text{mm min}^{-1})$$

The Student's t test, chi-squared test and Pearson product moment coefficient of correlation were used for statistical analyses.

RESULTS

The following indicators of slow mucociliary clearance were chosen after a review of the literature (Bang, Mukherju and Bang, 1967; Proctor, 1969; Friedman et al., 1977; Yergen et al., 1978; Puchelle et al., 1981): (1) an increase in transport time by 45% or more; (2) a decrease in transport velocity by 50% or more.

TABLE I. *Serial changes in nasal mucociliary clearance in the intubated nasal cavity*

	Normal clearance		Slow clearance	
	No.	%	No.	%
Before operation (control)	40	100	0.0	0.0
After operation				
Day 1	14	35	26	65
Day 3	16	40	24	60
Day 7	22	55	18	45
Day 10	36	90	4	10

TABLE II. *Mucociliary clearance before and after nasotracheal intubation*

	Day	Mucociliary clearance (mean ± SD)
Transport time (min)	Before operation (control)	25.8±0.8
	After operation	
	Day 3	37.9±1.3
	Day 7	32.8±1.2
	Day 10	27.1±0.6
Transport velocity (mm min⁻¹)	Before operation (control)	6.3±1.2
	After operation	
	Day 3	2.7±0.9
	Day 7	3.8±1.9
	Day 10	5.8±1.1

Clearance was considered abnormal only if the duplicate measurements were within 2% of their mean (Yergen et al., 1978).

Slow mucociliary clearance was observed in the intubated side of the nose in 26 patients (65%) on the 3rd day after intubation. There was gradual recovery during the next week. On the 10th day, only four patients (10%) still had evidence of slow clearance (table I). The means of the measurements are shown in table II. Analysis of the transport time and the transport velocity revealed a significant correlation between these two indices ($r = 0.89$; $t = 5.72$; $P < 0.001$).

No statistically significant differences could be shown between patients with normal and slow clearance rates with respect to age, sex and smoking history. Similarly, no differences could be detected between the two groups on the basis of size of tracheal tube or the use of lubricants. Difficult or prolonged intubation caused a statistically significant increase in the incidence of slow clearance (table III). The operative time, in particular, was positively correlated with prolongation of the transport time (fig. 2) ($r = 0.79$; $t = 2.55$; $P < 0.05$).

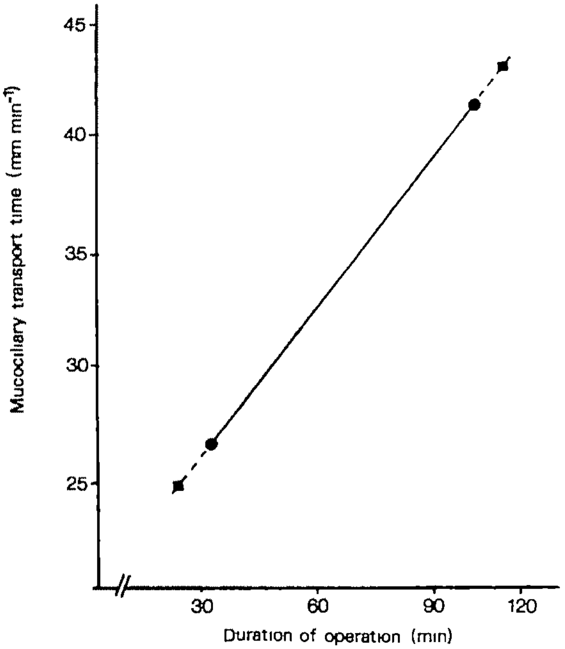

FIG. 2. Regression analysis of the mucociliary transport time (mm min⁻¹) against the operative time (min) depicting a linear relationship. The continuous line is the experimental line of best fit, the dotted line is calculated. Intercept = 17.2. Slope = 0.41.

TABLE III. *Significance of possible risk factors (based on measurements on the 1st day after operation).* P < *0.05 taken as significant*

Factor	Normal clearance ($n = 4$)	Slow clearance ($n = 26$)	Statistical significance
Age (yr)			
Mean	36.8	36.4	$P < 0.05$
Range	15–40	19–48	$t = 1.728$
Sex (No. patients)			
Male	6	18	$P < 0.05$
Female	8	8	$\chi^2 = 2.637$
Smoking history (No. patients)			
Yes	6	17	$P < 0.05$
No	8	9	$\chi^2 = 1.672$
Endotracheal tube size (No. patients)			
7	1	2	$P < 0.05$
8	3	6	$\chi^2 = 31.01$
8.5	7	11	
9	3	7	
Lubricant (No. patients)			
Used	6	14	$P < 0.05$
Not used	8	12	$\chi^2 = 1.963$
Nature of intubation (No. patients)			
Easy	12	13	$P > 0.05$
Difficult	2	13	$\chi^2 = 4.953$
Duration of operation (min)			
Mean	62	118	$P > 0.05$
Range	30–125	45–180	$t = 1.789$

DISCUSSION

Several methods have been described to evaluate the efficacy of nasal mucociliary transport (Proctor and Andersen, 1982). In this study, a modified radiopaque disc method was used and proved to be simple, easy to perform, and reliable. Stewart (1948) found that the weight of the discs applied to the nasal mucosa did not affect mucociliary transport up to a load of 20 mg mm^{-2}. The load of the discs used (2-5 mg mm^{-2}) was substantially less.

Hilding (1963) described a series of changes in the tracheal epithelium after minimal trauma. These took place during the first 24 h following injury and were characterized by progressive loosening of the epithelial cells. Regeneration of the epithelium started during the next 72 h. Collins (1980) mentioned that the tracheal tube frequently crushes the cilia and the superficial epithelial cells. Brondeel and colleagues (1983) reported prolongation of the saccharin and technetium resin transport times.

Unilateral slowing of mucociliary clearance, presumably as a result of damage to the epithelial cells by the tracheal tube, was observed in 65% of the patients studied. Recovery was complete by the 10th day after operation in 90% of these patients. Several possible risk factors were examined: age and sex were irrelevant. As has also been shown by Quinlan and colleagues (1969) and Simon, Drettner and Jung, (1977), there was no difference between smokers and non-smokers, but this may be attributed to the fact that the smokers included in the study were not heavy users of tobacco. The size of the tracheal tube was insignificant, but the size used was chosen with care. On the other hand, difficult intubation and prolonged operative times were associated with more mucociliary stasis, indicating more significant ciliary damage. This effect would probably be more serious if the tube was kept in place for several days. Severe destruction of the cilia would be anticipated under these circumstances.

In conclusion, slowing in mucociliary clearance was common after nasal intubation. For this, and other reasons (Collins, 1980), oral intubation is regarded as a safer procedure. Should nasal intubation be necessary, a proper choice of tube size and gentle manipulation are essential, if damage to the delicate respiratory nasal mucosa is to be avoided. In this context, the use of lubricants does not seem to preserve the integrity of the mucociliary transport mechanism. It may be that nasal intubation, for periods of time longer than those studied here, causes even more damage and this should be the subject of further research.

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TISSUE RESPONSES TO HYPEROXIA

Biochemistry and Pathology

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All tissues of the body, in the long term, require oxygen to sustain cellular integrity and effective organ function. At molecular level, oxygen is utilized primarily for the oxidation of substrates, and the associated production of energy used for ionic transport, contraction and biosynthesis. The four-electron reduction of dioxygen to yield energy during aerobic metabolism necessarily progresses through toxic free-radical intermediates (superoxide anion, hydrogen peroxide and hydroxyl radical). Although normally prevented from release to the components of the cell by the arrangement of the cytochromes, each intermediate can cause cellular damage, either directly or by the initiation of radical chain reactions. In addition, there are other sources of free radicals within cells: for example, during phagocytosis, the xanthine–xanthine oxidase system, or from the conversion of haemoglobin to methaemoglobin (Carrell, Winterbourne and Rachmilewitz, 1975). Hence, life within an oxygen-containing environment, whilst conferring advantages in terms of energy production, is not without its hazards. Red blood cells and cells of the lung (and possibly arterial endothelium), in particular, are unique within the body as they are exposed to the greatest oxygen tensions.

To combat the harmful effects of oxygen-derived free radicals, aerobic organisms have evolved elaborate protective mechanisms. These include enzymes (superoxide dismutase, catalase and glutathione peroxidase), thiol-containing compounds (reduced glutathione) as well as other antioxidants (eg. vitamins A, C and E).

SUMMARY

An animal model was established to study the toxic effects of hyperoxia and the consequent changes in intracellular antioxidant status. Superoxide dismutase, catalase and glutathione peroxidase activities were measured in erythrocytes, liver and lung, in addition to cellular glutathione concentrations and its associated metabolism. Overt cellular damage was assessed biochemically by measurement of lipid peroxidation, hydrogen peroxide-induced haemolysis and osmotic fragility. Pathological changes were assessed by light and electron microscopy. Up to 11 days exposure of rats to 80% oxygen was not lethal, but resulted in overt cellular damage to red blood cells (haemoglobin concentration decreased from 13.8 ± 1.4 (SD) g dl^{-1} to 12.4 ± 0.5 g dl^{-1}; hydrogen peroxide-induced haemolysis increased from 7.7 ± 1.6% to 75.1 ± 13.5% after 11 days of hyperoxia) and to cells of lung (4-fold increase in lipid peroxidation) as well as a biochemical adaptation to the increased concentration of oxygen metabolites (superoxide dismutase increased 3-fold, catalase 5-fold and glutathione peroxidase 2-fold). It is suggested that red cell hydrogen peroxide-induced haemolysis and reduced glutathione concentration may be useful indicators of oxidant stress in the clinical situation.

Although it is widely accepted that structural and functional changes occur in the lungs of animals exposed to increased oxygen tensions, there is as yet no conclusive evidence that these are caused by oxygen-derived free radical species. However, it has been shown that, at increased Po_2, there is enhanced production of superoxide anion and hydrogen peroxide in lung mitochondria and

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microsomes (Turrens et al., 1982; Turrens, Freeman and Crapo, 1982) and it seems very likely that these and other species are the mediators of oxygen toxicity.

It is not possible to measure the concentrations of oxygen-derived free radical species *in vivo*. However, it is possible to measure the activities of the enzymes responsible for the detoxification of these radicals (superoxide dismutase, catalase and glutathione peroxidase). The activities of such enzymes will reflect changing substrate concentrations. In addition, there are several markers of oxidant damage which can be determined (products of peroxidation and hydrogen peroxide-induced haemolysis) which provide evidence of increases in the concentrations of free radicals.

Various workers, cited in the discussion below, have reported the response to increases in Po_2 of one or other of these indices of oxidant damage in single organs or cell cultures, but there has been no integrated study of the response of the full range of antioxidant enzymes, together with a number of markers of oxidant damage in several organs, in the intact animal exposed to hyperoxia. Such a study would provide evidence of increased free radical concentrations *in vivo*, as well as suggesting markers of oxidant damage to be used in investigations in man. We have, therefore, examined the changes in lung, liver and red blood cells in the rat exposed to 80% oxygen for up to 11 days. The antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and the concentration of the antioxidant reduced glutathione (GSH), as well as the enzymic pathway responsible for its regeneration, were measured. In addition, the markers of injury, hydrogen peroxide haemolysis, osmotic fragility and lipid peroxidation were examined, along with histological changes in the lungs of rats exposed to oxygen.

MATERIALS AND METHODS

Young adult male Wistar rats (weight 175–225 g) reared under specific pathogen-free conditions were placed in a cage within a Perspex enclosure. Gas mixtures were delivered to the enclosure at a flow rate selected to provide four to five total enclosure washouts per hour, so that adequate removal of carbon dioxide could be achieved (carbon dioxide content less than 1%). Gases used were either a mixture of 80% oxygen and 20% nitrogen (British Oxygen Special Gases Division) or air. We selected 80% oxygen as the greatest concentration compatible with survival in this species. Oxygen and carbon dioxide tensions were assessed by gas sampling from the enclosure after 24 h using a glass syringe and Corning 175 blood-gas analyser.

Animals were kept continuously in this environment for 0 ($n = 22$), 3 ($n = 9$), 5 ($n = 12$), or 11 ($n = 6$) days, except for short periods each day (10 min maximum) to permit cleaning and administration of fresh food and water. A cycle of 12 h light and 12 h darkness was adhered to. Feed (CRM pelleted diet (Labsure, Cristopher Hill Group)) and water were allowed *ad libitum*. A control group of animals ($n = 22$), which were exposed to air in the Perspex enclosure for 5 days, was included.

Following predetermined periods of exposure, rats were removed from the exposure chamber and anaesthetized with chloroform. An incision was made in the anterior abdominal wall, the aorta cannulated and 6 ml of blood taken in a heparinized syringe and collected into a tube containing EDTA as anticoagulant. The chest was then opened, the pulmonary artery cannulated and the left atrium drained. Blood was then washed from the pulmonary circulation with 5 ml of isotonic saline. The heart, lungs and trachea were removed. A sample of liver (approximately 0.5 g) was taken for examination. Lung was dissected free of heart, major vessels and fatty tissue, blotted dry and weighed.

Tissue preparation and histology

Blood. With the exceptions outlined below, all assays were performed on saline-washed red cells. Haemolysates for enzyme assays were prepared in mercaptoethanol EDTA stabilizing solution (Beutler, 1975). Whole unwashed blood was used for the estimation of the concentration of reduced glutathione and the determination of osmotic fragility and hydrogen peroxide haemolysis.

Lung and Liver. The left main bronchus was ligated and the left lung removed distal to the ligature. The right lung was inflated to 5 cm H_2O pressure with 10% neutral buffered formalin (pH 7.0) and maintained at this pressure for 5 min; the tissue was then placed in neutral buffered formalin to await histological examination. The left lung and liver sample were each placed in 10 ml of 50-mmol litre^{-1} phosphate buffer (pH 7.5) and homogenized using an ultrasonic homogenizer. Care was taken to ensure that samples did not overheat, by surrounding them with ice and using three 30-s pulses. The homogenates were cleared of cell debris by centrifugation at 400 rev min^{-1} for 10 min and biochemical assays carried out as described below.

Histological examination was performed with the treatment schedule not being disclosed until after reporting. After fixation in neutral buffered formalin solution, samples for light microscopy were prepared using the standard 18-h paraffin embedding process, with sections cut at 5 µm. Stains used were haematoxylin and eosin, Marteus-Scarlet-Blue, Gordon and Sweet's reticulin, and a peroxidase stain (Drury and Wallington, 1967). The degree of pulmonary oedema observed on light microscopy was quantified using the following scoring system: no oedema = 0; slight oedema (broncho-vascular interstitial oedema) = 1; severe oedema (intra-alveolar flooding) = 2.

Fresh lung specimens (approximately 1.0 mm^3) for electron microscopy were fixed in glutaraldehyde solution (3% w/v) and stained using Reynold's lead citrate and uranyl acetate reagent.

Chemical estimations

Haemoglobin concentration and red cell count of whole blood were determined by Coulter counter.

Protein content of lung and liver homogenates was determined by the method of Lowry and colleagues (1951), using human albumin as standard.

Lipid peroxidation was assessed on the 5th day of exposure by measuring the formation of malondialdehyde (MDA) when lung and liver homogenates were allowed to react with thiobarbituric acid in hydrochloric acid (Buege and Aust, 1978). Results are expressed as MDA nmol/g protein.

Reduced glutathione (GSH) was estimated in whole blood and tissues by the method of Beutler (1975). The assay uses as chromophore 5,5′-dithiobis (2-nitrobenzoic acid) (DTNB); this is reduced by sulphydryl compounds to form a highly coloured yellow anion. The assay is specific for GSH in red cells as virtually all of their non-protein sulphydryl content is present as reduced glutathione. GSH concentration was expressed as µmol/g haemoglobin (blood), or µmol/g wet tissue weight (lung and liver).

Red cell assays

Hydrogen peroxide haemolysis was measured by incubating a suspension of washed red blood cells in hydrogen peroxide (Gordon, Nitowsky and Cornblath, 1955; Nitowsky, 1956).

Osmotic fragility was assessed by the method of Dacie and Lewis (1970) on whole unwashed blood.

Pentose phosphate pathway activity was estimated using a method which measures ^{14}C-carbon dioxide released when red cells metabolize ^{14}C-glucose labelled in the C1 position. Both stimulated (by the addition of methylene blue) and unstimulated activities were determined. This test is specific for the pentose phosphate pathway (PPP) in the case of red blood cells because of their lack of enzymes for oxidative phosphorylation. PPP activity was expressed as the percentage of carbon-14, added as ^{14}C-1-glucose, which was recovered ^{14}C-carbon dioxide per 3 h per red cell ($^{14}CO_2$/3 h/red cell).

Enzymes

Glucose-6-phosphate dehydrogenase (G-6-PD), 6-phosphogluconate dehydrogenase (6-PGD), NADPH-diaphorase (NADPH-D), catalase (CAT) and glutathione peroxidase (GPX) were estimated by the method of Beutler (1975). Results were expressed as iu/g haemoglobin (red cell), or iu/g protein (lung and liver).

Superoxide dismutase (SOD) activity was estimated by the method of Crapo, McCord and Fridovich (1978). Xanthine 0.5 mmol $litre^{-1}$ and xanthine oxidase were used to generate superoxide anion at a constant rate, and ferricytochrome c 0.1 mmol $litre^{-1}$ was used to detect superoxide anion. With liver extracts it was found necessary to add 10 µl of 3-mmol $litre^{-1}$ potassium cyanide (to inhibit interference from cytochrome oxidase) and 10 µl of catalase 10000 iu ml^{-1} (to inhibit interference from cytochrome c peroxidase) to the reaction mixture.

In some samples of lung and liver homogenate taken after 5 days exposure, the relative contributions of CuZn- and Mn- forms of SOD to the total SOD activity were determined. This was accomplished by performing the assay in the presence of potassium cyanide 1 mmol $litre^{-1}$, which inhibits CuZn-SOD by about 90%. Mn-SOD was determined by subtracting the CuZn-SOD from the total SOD activity. One unit of SOD activity is that activity which results in a 50% inhibition of the rate of the control reaction. Results are expressed as u/g haemoglobin (red cell), or u/g protein (lung and liver).

Statistical analysis

Results were compared by the Mann–Whitney *U* or the Kruskal–Wallis statistic for non-parametric data, or by Student's *t* test, as appropriate (Sachs, 1982). Results shown are mean ± SEM; $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ are significantly different from control.

RESULTS

Histology

Haematoxylin and eosin staining revealed both interstitial and intra-alveolar oedema in all oxygen exposed groups, but no significant further increase was noted with treatment for more than 24 h (table I). Peroxidase staining for lysozyme failed to detect an increase in the number of macrophages in lung sections from treated animals, and the absence of fibrin deposition was confirmed by MSB staining.

Electron microscopy of sections of lung from control and 11-day oxygen-treated animals revealed a significant increase in the ratio of type II to type I pneumocytes in the oxygen-treated rats. Furthermore, there was an increase in the number of lamellar bodies within the type II cells of treated animals (table II).

Chemical estimations

Haemoglobin concentrations were significantly decreased with oxygen exposure: control was 13.8 ± 1.4 (SD) g dl^{-1}, 3 days exposure 13.4 ± 0.9 g dl^{-1}, 5 days exposure 12.4 ± 0.5 g dl^{-1} ($P < 0.001$), and at 11 days exposure 11.9 ± 0.6 g dl^{-1} ($P < 0.001$).

Protein. Lung weight increased by 28% at the 3rd day of exposure to 80% oxygen and no further increase occurred with longer exposures (table III). Protein content, expressed as mg per lung wet weight, remained constant, with the exception of a significant reduction at day 5. However, when expressed as mg/g lung wet weight, there was a significant reduction with all times of exposure to hyperoxia studied.

Lipid peroxidation. The increase in products of peroxidation measured at the 5th day (fig. 1) was significant ($P < 0.001$) in both tissue homogenates.

TABLE I. *Severity of pulmonary oedema produced by exposure of rats for varying periods, to an 80% oxygen : 20% nitrogen mixture. Pulmonary oedema was determined by light microscopy of haematoxylin and eosine-stained lung specimens. Scores: 0 = no oedema; 1 = mild oedema; 2 = severe oedema (results for rats in each group were summated and a mean determined)*

Exposure to 80% oxygen (days)	*n*	Oedema score
0	13	0.0
1	7	1.2
2	6	1.0
3	5	1.0
11	6	1.6

TABLE II. *Electron microscopic changes in alveolar type I and type II cells produced by oxygen exposure. Rats were exposed to an 80% oxygen : 20% nitrogen mixture for 11 days and the electron microscopic appearance of lung specimens compared with those of air-breathing animals. Representative fields from each group were examined at the same magnification and the total number of type I and type II cells, and the number of lamellar bodies within each type II cell, determined.* $^{*}P < 0.05$; $^{**}P < 0.01$

	Air	80% Oxygen
Fields inspected	15	12
Type II/type I cell ratio	0.20 ± 0.02	0.56 ± 0.05**
Lamellar bodies per type II cell	7.80 ± 0.77	9.95 ± 1.02*

TABLE III. *Changes in lung weight and protein from rats exposed to an 80% oxygen : 20% nitrogen mixture for 3, 5, and 11 days when compared with air control animals (0 days). Results are mean ± SEM.* $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

Exposure to 80% oxygen (days)	*n*	Lung wet weight (g)	Total lung protein (mg)	Total lung protein (mg g^{-1})
0	22	1.08 ± 0.03	154 ± 8	143 ± 8
3	9	1.23 ± 0.15*	134 ± 12	109 ± 9*
5	12	1.25 ± 0.03**	123 ± 5*	98 ± 9**
11	6	1.34 ± 0.04***	142 ± 17	101 ± 12**

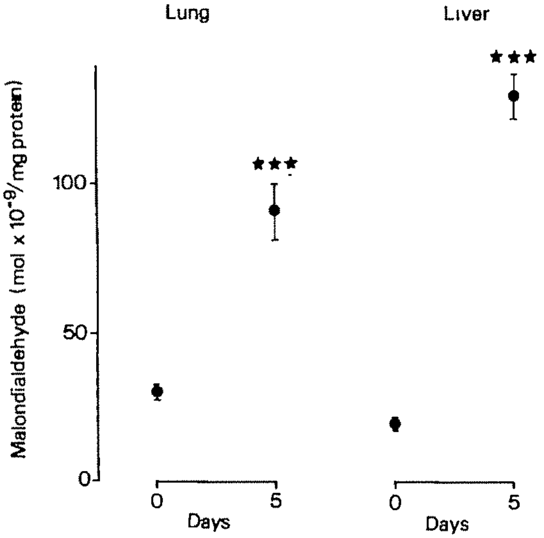

FIG. 1. Lung and liver lipid peroxide concentrations (TBA reactive compounds) from rats breathing air (0 days) and after 5 days exposure to 80% oxygen. Results are expressed as malondialdehyde mol × 10^{-9}/mg protein.

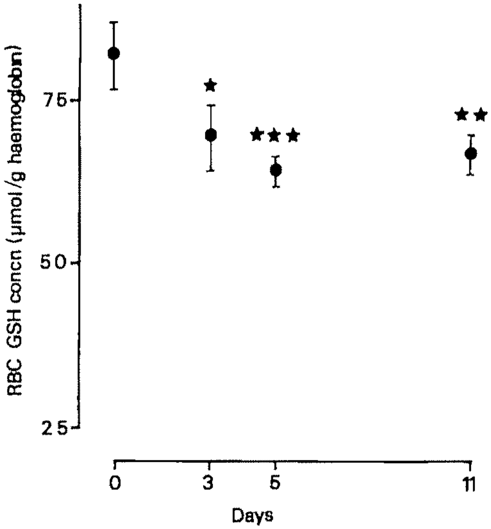

FIG. 2. Red cell reduced glutathione concentrations in rats exposed to 80% oxygen for 3, 5 and 11 days compared with those in rats breathing air (0 days).

Reduced glutathione concentration. Six rats exposed to 80% oxygen in nitrogen for 5 days had concentrations of reduced glutathione in lung of 0.48 ± 0.06 µmol/g wet weight; this was unaltered from animals breathing 21% oxygen (air controls): 0.53 ± 0.06 µmol/g wet weight.

Persistent, and small but significant, decreases ($P < 0.05$, $P < 0.001$ and $P < 0.01$ at 3, 5 and 11 days, respectively) were noted in red cell reduced glutathione concentrations with oxygen treatment (fig. 2).

Red cell assays

Hydrogen peroxide haemolysis. There was a steady increase in hydrogen peroxide haemolysis with increasing durations of exposure to oxygen (fig. 3), indicating a progressive inability of the red cell to withstand sustained oxidative stress ($P < 0.001$).

Osmotic fragility. Red blood cells from rats exposed to 80% oxygen for 5 days were less fragile than those from control animals (fig. 3).

Pentose phosphate pathway. Stimulated and unstimulated activities of the pentose phosphate pathway were decreased following treatment with oxygen for 3 and 5 days ($P < 0.05$ and 0.01; and $P < 0.01$ and 0.01, respectively), although activity in both cases had returned virtually to normal after 11 days treatment (fig. 4). G-6-PD and NADPH-D activities were increased in the experimental animals at 5 days exposure (fig. 5).

Enzyme assays

Significant increases in the activities of SOD (3-fold), CAT (5-fold) and GPX (2-fold) in lung were noted, whilst increases in the activity of SOD and CAT only were demonstrable in liver (figs 6–8). Red cell GPX activity decreased with exposure to oxygen with no statistically significant change in either SOD or CAT activities.

All three enzymes had a higher activity in liver than in lung; the most marked difference was seen with catalase, where activity in liver was approximately 30 times that in lung, compared with three times for SOD and GPX.

There was also a wide difference in activities of GPX and CAT between the tissues studied, with lung having 1000 times more GPX activity than CAT activity, and the red cell having 100 times more CAT activity than GPX activity.

No one form of SOD was responsible for the increase in total SOD activity seen in either lung or liver, as both the CuZn and Mn forms increased by the same relative amounts (fig. 9).

DISCUSSION

Previous workers have reported changes in some or all of the antioxidative systems in a variety of

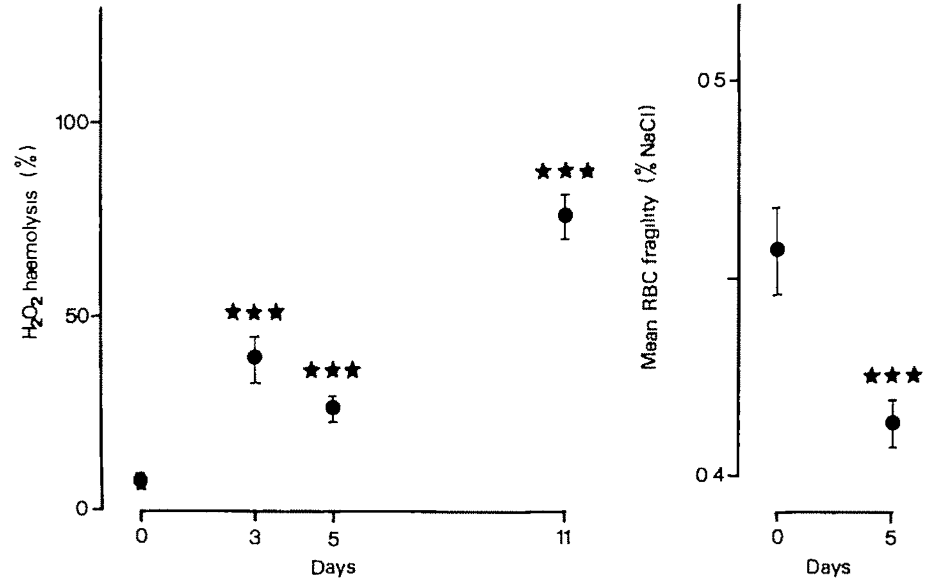

FIG. 3. Red blood cell hydrogen peroxide haemolysis and osmotic fragility of rats breathing 80 % oxygen for up to 11 days, compared with air-breathing controls (0 days). Results are expressed as percentage of the fully haemolysed sample (for H_2O_2 haemolysis) and the concentration of saline producing 50 % haemolysis (mean RBC osmotic fragility).

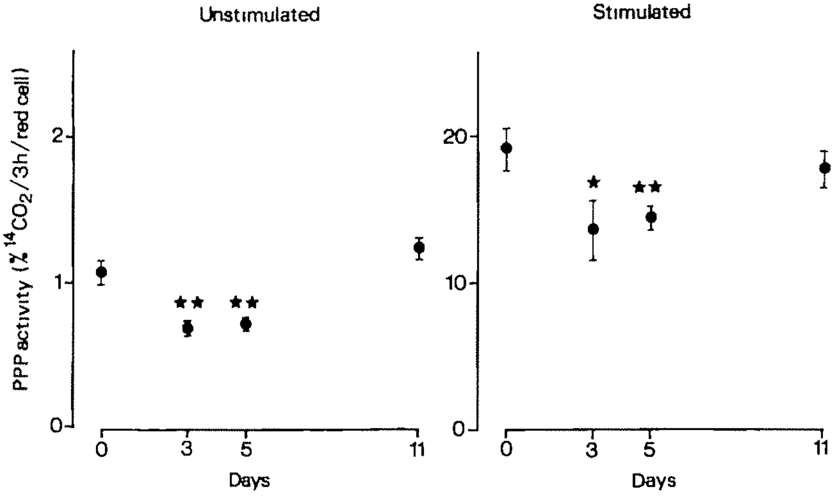

FIG. 4. Red blood cell pentose phosphate pathway (PPP) activity of rats breathing 80 % oxygen for 3, 5 and 11 days compared with air breathing controls (0 days). Both stimulated (by addition of methylene blue) and unstimulated PPP activity are shown. Results are expressed as the percentage of carbon-14 added as ^{14}C-1-glucose which was recovered as $^{14}CO_2$/3 h/red cell × 10^{-9}.

tissues, but none has looked at them all in lung, liver and red blood cells. Moreover, none has associated changes in red blood cells with those in the lung. Such red cell biochemical markers reflecting oxidative damage within the lung may prove useful as monitors of the clinical situation.

The weight of lung varies with oxygen exposure as a result of the accumulation of oedema. An increase in lung weight of 28 % was observed at 3 days, and this then remained virtually constant (table I). Crapo and Tierney (1974) observed a 45 % increase in lung weight after 7 days exposure

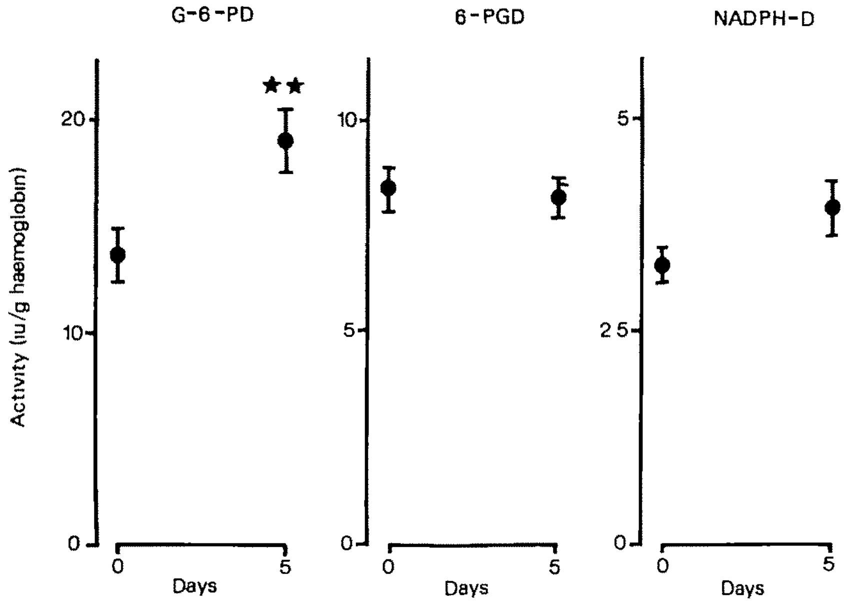

FIG. 5. Glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase and NADPH-diaphorase activities in red blood cells taken from rats breathing 80% oxygen for 5 days. For comparison, results from rats breathing air only are also shown (0 days).

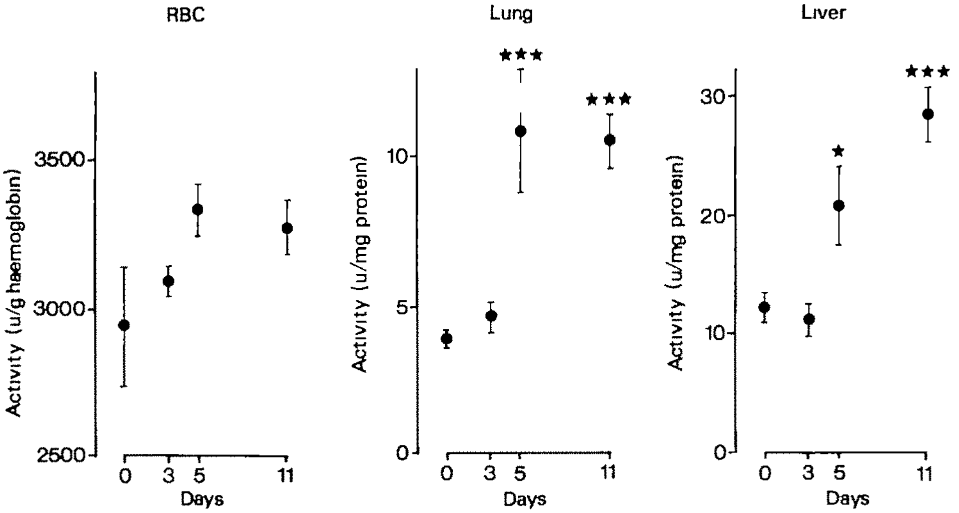

FIG. 6. Superoxide dismutase activity in red blood cells and tissues taken from rats exposed to 80% oxygen for periods up to 11 days. For comparison, results from rats breathing air only are also shown (0 days).

to 85% oxygen. However, in contrast to the present study where a decrease in total lung protein of 35% was seen following 5 days exposure to oxygen, Crapo and Tierney (1974) observed an increase (68%) in lung protein after 7 days exposure. The additional 2 days may be significant as, in the present study, total lung protein had returned to control values by 11 days. These workers offered no explanation for these changes. Moreover, these workers observed no

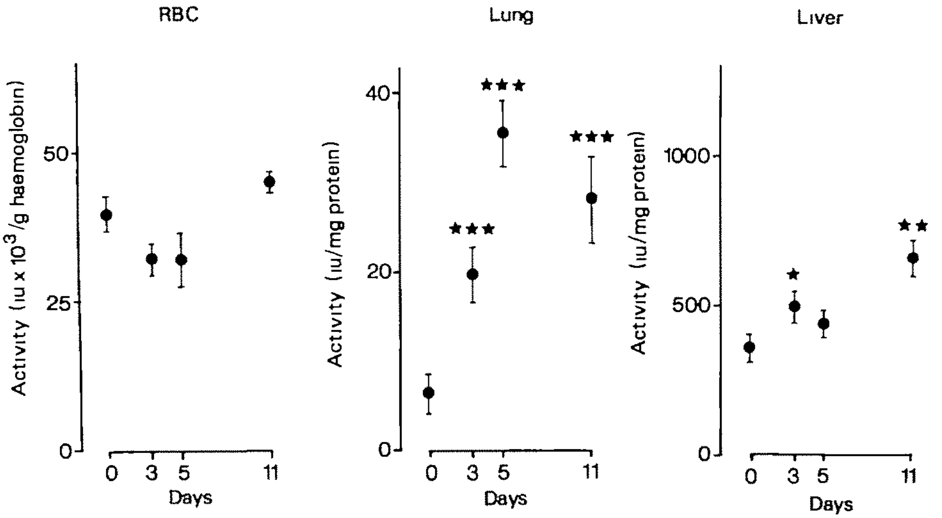

FIG. 7. Catalase activity in red blood cells and tissues taken from rats exposed to 80% for periods up to 11 days. For comparison, results from rats breathing air only are also shown (0 days).

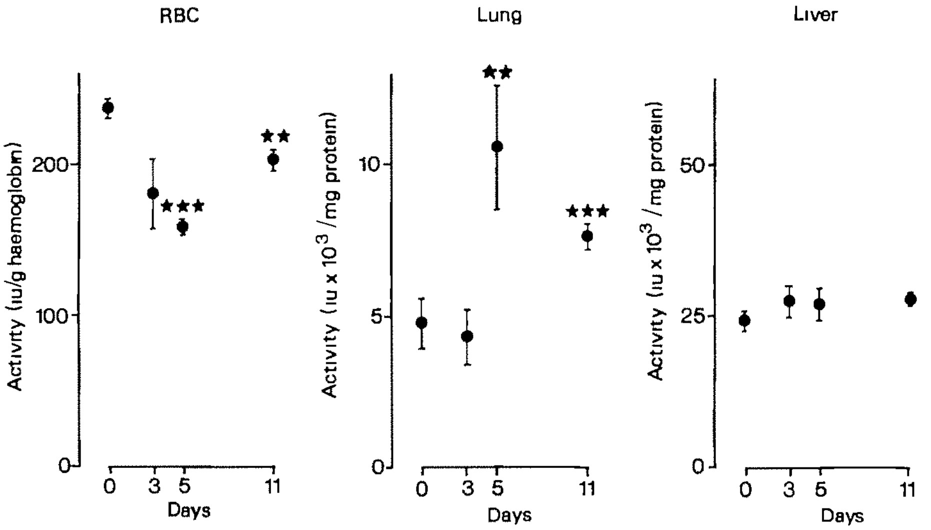

FIG. 8. Glutathione peroxidase activity in red blood cells and tissues taken from rats exposed to 80% oxygen for periods up to 11 days. For comparison, results from rats breathing air only are also shown (0 days).

change in total DNA content of lung after the 7-day exposure period, which suggests that there was no significant change in cell numbers.

Lung superoxide dismutase activity in the present study increased 3-fold, with similar changes in both the CuZn and Mn forms of SOD (figs 6 and 9), this was maximal at 5 days in lung and was still increased at 11 days. The response in liver occurred more slowly, with activity increasing further between days 5 and 11. Again the increase was similar in both forms of SOD. Kimball and colleagues (1976) also found similar changes in SOD activity of lung mitochondrial and cytosolic fractions in rats exposed to 90% oxygen. In another study (Crapo et al., 1980) there was a 42% increase for CuZn-SOD and 75% for

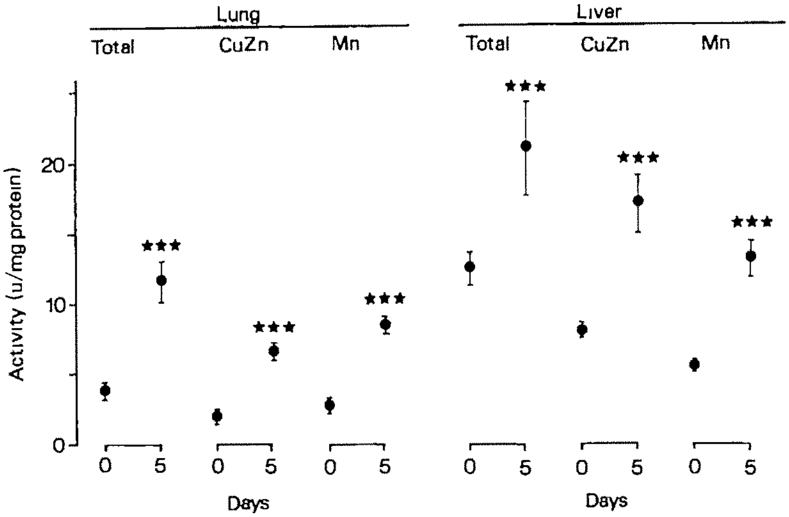

FIG. 9. Tissue CuZn- and Mn-superoxide dismutase activities in lung and liver from rats exposed to 80 % oxygen for 5 days. Lung and liver from animals exposed to air only were used as controls and results appear at time 0.

Mn-SOD activity in lung after 5 days exposure. Crapo and Tierney (1974) examined the changes in SOD activity in several tissues including lung, liver and whole blood, finding demonstrable differences between exposed and unexposed rats only in the case of lung and brain, where activity was increased, and in liver, where activity was significantly decreased. No change in red cell SOD activity was reported by these workers. In the present study an increase was noted, although this was not statistically significant. Red blood cells have no DNA or RNA and cannot synthesize protein. However, the red cell population changes and a new generation could have higher SOD activities. Another possibility would be the change in specific activity that could be produced by enzyme amplification.

The liver responds to oxidant stress in a manner similar to the lung, with SOD activity increasing by 67 % and 130 % after 5 and 11 days exposure to oxygen, respectively. This finding is in contrast to that of Crapo and Tierney (1974), who observed a decrease in liver SOD activity. One reason for this difference may be the units used to express enzyme activity, Crapo and Tierney (1974) giving units of activity per organ wet weight, as opposed to our units per milligram of protein. In addition, in the present study it was found necessary to use the assay modification developed by Crapo, McCord and Fridovich (1978) to overcome interference by cytochrome oxidase and cytochrome c peroxidase. There was no mention of this modification being used by Crapo and Tierney (1974).

The presence of increased concentrations of intracellular superoxide anion inevitably results in increases in peroxide concentrations. Although it is now accepted that, under normal circumstances, glutathione peroxidase is probably the main enzyme responsible for the removal of organic peroxides, catalase has an important role in the detoxification of hydrogen peroxide. Lung CAT activity was found to increase by 75 % after 5 days (fig. 7). Steinberg and co-workers (1983) also showed an increase of 80 % after 7 days exposure. Activity of catalase in liver increased more slowly, by 45 % of control values after 11 days. The slower response of liver compared with lung was seen with both SOD and CAT. There was no significant effect of exposure to oxygen on red cell CAT activity.

Both Kimball and colleagues (1976) and Ospital, Kasumaya and Tierney (1983) found increases in lung GPX activity (approximately 120 % after 7 days) with oxygen exposure. A similar change was noted earlier (at 5 days) in the present study but, unlike catalase, no change was observed in GPX activity in liver. This suggests that catalase is more important than GPX in the liver of animals exposed to oxygen, perhaps as a result of the preferential accumulation of hydrogen peroxide rather than organic peroxides.

The greater activity of CAT in red cells than GPX (100 times) suggests that this cell is particularly well adapted to cope with increases in hydrogen peroxide concentration. On account of the large turnover of methaemoglobin (approximately 3% of total body haemoglobin per day) (Carrell, Winterbourne and Rachmilewitz, 1975), and the high content of iron, probably the major toxic oxygen-derived species within the red cell are the hydroxyl radical and hydrogen peroxide. This is unlike lung and liver, where GPX activity is approximately 100–1000 times that of CAT and organic peroxides would appear to be the principal toxic agents.

Red cell G-6-PD activity was increased by 45%, while 6-PGD and NADPH-D activities remained constant, after 5 days exposure to 80% oxygen (fig. 5). Kimball and colleagues (1976) and Ospital, Kasumaya and Tierney (1983) found greater increases in lung G-6-PD activity: 250% and 189%, respectively.

A 2-fold increase in products of peroxidation in lung homogenates was found in the present study after 5 days oxygen exposure (fig. 1). We are in close agreement with Freeman, Topolosky and Crapo (1982), who reported a 150% increase in TBA reactive material in lung taken from rats exposed to increased oxygen tensions. The increase (by 550%) of peroxidation products in liver lends support to the hypothesis that the liver also can be adversely affected by oxygen.

After taking into consideration the glutathione content of residual red blood cells in tissues, it was noted that reduced glutathione concentration was much lower in lung than in liver. Concentrations in lung were unaltered in rats exposed to 80% oxygen for 5 days. Kimball and colleagues (1976) showed an increase in total thiol content in lung following 5 days exposure. However, the actual concentration of reduced glutathione reported was 1.17 ± 0.18 μmol/lung—a value double that seen in the present study. This difference could be explained by red cell contamination.

The concentration of red cell reduced glutathione was decreased significantly with oxygen exposure. This is probably a result of oxidation of red cell components, with oxidized glutathione rapidly leaving the red cell by an active membrane-bound transport system. This would be expected to occur largely at the beginning of the period of exposure, as tensions around the red cell would then be greatest. Later, blood oxygen tension would decrease as a result of the defective diffusion of oxygen across the alveolar membrane as a result of the accumulation of oedema fluid. This may explain why the reduced glutathione concentration decreased significantly after 3 days and then remained constant.

Reduced glutathione (GSH) is a major low molecular weight intracellular antioxidant. It is oxidized to GSSG either directly, or indirectly, by acting as cofactor for the enzyme glutathione peroxidase. This oxidation results in an unfavorable GSH:GSSG ratio. GSH is regenerated from GSSG by glutathione reductase, and this enzyme has a requirement for NADPH which is derived largely from the metabolism of glucose-6-phosphate via the pentose phosphate pathway. At 3 and 5 days exposure, when GSH concentrations were lowest, red cell PPP activity, both stimulated and unstimulated, was significantly reduced from control values, activity returning to normal after 11 days exposure.

In view of the recorded decrease in red cell glutathione peroxidase activity, PPP activity and reduced glutathione concentration, it would appear that at 5 days, GSH is not the major defence of the red cell to oxidant stress. It is possible that some other substance, such as vitamin E, is used at this stage. Increased hydrogen peroxide haemolysis has been reported with vitamin E deficiency (Nitowsky, 1956). The observed increase in hydrogen peroxide haemolysis (fig. 2) supports this point. With minor changes in the measured red cell antioxidants, the erythrocyte membrane was unable to withstand further oxidative stress. This change was not the result of overt structural damage, as osmotic fragility was, surprisingly, decreased after 5 days exposure to oxygen. One explanation may be that peroxidation of the red cell lipid results in a stiffer membrane with altered ion and water transfering capacity (Sheridan and Block, 1985).

The occurrence of interstitial oedema in the broncho–vascular bundle was a constant finding in the lungs of oxygen-treated rats. Oedema accumulated rapidly, being found after only 24 h exposure to 80% oxygen. However, even at 11 days, no increase (from control animals) could be detected in fibrin deposition. These findings are in agreement with other reports (Kimball et al., 1976; Crapo et al., 1980; Hayatdavoudi et al., 1981; Johnson et al., 1981) and lead to the suggestion that the initial site of injury is the pulmonary capillary endothelium.

In electron microscopy specimens examined after 11 days exposure to oxygen, an increase in alveolar type II cells was observed (table II). Crapo and co-workers (1980) also observed this change following treatment with oxygen, suggesting this to be a repair process—both to maintain the alveolar integrity and, perhaps, to assist the biochemical response. In this respect useful information may be obtained by comparing the antioxidant enzyme responses of alveolar type I and type II cells to 80% oxygen. Type II cells are known to be biochemically active and it is possible that they have higher activities of antioxidant enzymes. Enzyme changes noted in the whole lung may thus be entirely attributable to an increase in type II cell numbers. Forman and Fisher (1981), who examined alveolar type II cells from oxgyen-treated and control rats found that only CuZn-SOD was increased; all other enzymes investigated (Mn-SOD, catalase, GPX and G-6-PD) remained unaltered. As these workers expressed their results both as units/mg protein and units/mg DNA, it is possible that absolute numbers of type II cells may be an important factor. Some adaptation, however, obviously occurs within the type II cell, as an increase in the number of lamellar bodies within their cytoplasm was observed (table II). This may possibly be an attempt of the type II cell either to increase the total amount of pulmonary surfactant, or to replace that lost as a result of increased lipid peroxidation.

Our results suggest various possibilities for the prevention of oxygen-induced pulmonary damage. It would be logical to imitate the biochemical response seen in this study by the parenteral administration of SOD, with either CAT or GPX. However, these enzymes which act intracellularly have a half-life in plasma of only a few minutes (Huber and Saifer, 1977) and do not readily cross the cell membrane into the cytoplasm. Attempts to solve this problem have been made and liposome-entrapped SOD has been shown to reduce oxygen-induced damage to cultured endothelial cells (Freeman, Young and Crapo, 1983). Liposomes readily become incorporated within cell membranes, with discharge of their contents into the cytosol. This permits not only modification of the intracellular antioxidant activity, but also alteration of the cell membrane lipid composition. McDonald and colleagues (1985) suggested that conjugation with polyethylene glycol is a preferable method of delivery of antioxidant enzymes.

Treatment with antioxidants and free radical scavengers other than enzymes is another possibility. Again, delivery to the cell in sufficiently high concentrations is a potential problem and many of these compounds have their own problems of toxicity. Moreover, the use of such agents may suppress the response of endogenous antioxidants and may result in enhancement of the pathological changes.

In conclusion, a wide range of biochemical changes has been demonstrated in the lungs of rats exposed to 80% oxygen, some of which are paralleled by changes in the red cell. There is a wide interspecies variation in sensitivity to oxygen and, for obvious reasons, biochemical changes in the lungs of humans exposed to hyperoxia have not been determined. Any extrapolation of our findings in the rat to the human should, therefore, be made with caution.

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MUTAGENICITY OF THE COMBINATION OF A VOLATILE ANAESTHETIC AND NITROUS OXIDE

J. M. BADEN AND Y. R. KUNDOMAL

SUMMARY

The mutagenic potential of halothane, enflurane and isoflurane in combination with nitrous oxide was investigated using the sex-linked recessive lethal assay in the fruit fly Drosophila melanogaster. *Male wild-type flies were exposed for 1 h to 1 or 2% volatile anaesthetic with various concentrations of nitrous oxide up to 75%. They were then mated with untreated females of the Basc marker strain. A brooding pattern was used to assess mutagenicity at different germ cell stages. The rate of lethal mutations was assessed in the* F_2 *generation. Halothane produced a dose-dependent increase in the rate of lethal mutations, but the mutagenicity was independent of the presence of nitrous oxide and of the stage of germ cell formation. Neither enflurane nor isoflurane was mutagenic in the presence of nitrous oxide.*

The mutagenic potential of inhaled anaesthetics has been investigated extensively over the past decade (Baden and Rice, 1986). The most recently introduced volatile anaesthetics, isoflurane and enflurane, are not mutagenic when examined in various systems using single- and multi-cell organisms. Halothane, which is still widely used in many countries, is not mutagenic except in a sex-linked recessive assay using the fruit fly, *Drosophila melanogaster*. Although these anaesthetics, and many others, have been tested alone, they are usually administered clinically with nitrous oxide. To date, no information exists on the mutagenic potential of such combinations. The present study was undertaken to examine the mutagenicity of halothane, isoflurane and enflurane in combination with nitrous oxide.

MATERIALS AND METHODS

Mutagenicity was assessed in *Drosophilia melanogaster* using the sex-linked recessive lethal assay which has been described previously in detail (Kundomal and Baden, 1985). Briefly, two strains of *Drosophila* were used: the Oregon K, a wild-type with red, round eyes, and Basc, a marker stock carrying genes for bar and apricot eyes. Male wild-type flies, 2–3 days old, were exposed in sealed 11-litre desiccators for 1 h to 1 or 2% halothane in combination with 0, 25, 50 or 75% nitrous oxide. Since enflurane and isoflurane are not mutagenic when tested alone in *Drosophila* (Kundomal and Baden, 1985), they were screened only at the greater concentrations of 2% in combination with 75% nitrous oxide. Control groups of flies were exposed to room air alone. Other groups were exposed at the same time to nitrous oxide, enflurane or isoflurane alone. They served as controls for this and a previous study, the results of which have been reported previously (Kundomal and Baden, 1985). During exposure, the concentration of oxygen was monitored by an IL 402 oxygen monitor (Instrumentation Laboratory, Lexington, Massachusetts) and maintained at 21±1%. The balance of gas in the desiccators was nitrogen. Anaesthetic concentrations were measured at the start and end of exposure using gas chromatography or infra-red gas analysis and were always within 5% of the desired values. The temperature was maintained at 25±1 °C and the relative humidity was maintained at 50±5%.

Immediately following exposure, 30 male flies from each treatment group were selected at

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TABLE I. *Sex-linked recessive lethals following exposure of male* Drosophila melanogaster *to various volatile anaesthetic–nitrous oxide combinations.* **Significant increase above control:* $P < 0.05$

Treatment	Concentration of anaesthetics (vol %)	Brood	No. chromo. tested	No. lethals detected	Percent lethals calculated
Control	0/0	1	611	1	0.16
		2	618	2	0.32
		3	598	1	0.16
		1–3	1827	4	0.22
Hal/N_2O	1/0	1	603	6	0.99*
		2	609	4	0.65*
		3	618	7	1.13*
		1–3	1830	17	0.92*
	1/25	1	610	6	0.98*
		2	598	5	0.83*
		3	592	6	1.01*
		1–3	1800	17	0.94*
	1/50	1	600	7	1.16*
		2	601	7	1.16*
		3	603	5	0.82*
		1–3	1804	19	1.05*
	1/75	1	603	4	0.66*
		2	607	7	1.15*
		3	609	5	0.82*
		1–3	1819	16	0.87*
	2/0	1	606	9	1.48*
		2	601	10	1.66*
		3	607	8	1.31*
		1–3	1814	27	1.48*
	2/25	1	611	10	1.63*
		2	596	11	1.84*
		3	603	7	1.16*
		1–3	1810	28	1.54*
	2/50	1	605	11	1.81*
		2	609	7	1.14*
		3	602	9	1.49*
		1–3	1816	27	1.48*
	2/75	1	601	9	1.49*
		2	609	10	1.64*
		3	607	10	1.64*
		1–3	1817	29	1.59*
Enf/H_2O	2/75	1	603	0	0.00
		2	611	1	0.16
		3	599	1	0.16
		1–3	1813	2	0.11
Iso/N_2O	2/75	1	604	0	0.00
		2	601	2	0.33
		3	597	3	0.50
		1–3	1802	5	0.27

random. Each male was individually mated with three untreated virgin female flies of the Basc strain in individual vials with fresh medium (Carolina Biological Supply, Burlington, North Carolina). Three days after mating and after the eggs were deposited (first brood), female flies were discarded and male flies were immediately mated individually with three fresh Basc females in new vials to produce the second brood. Three days later, the mating procedure was repeated to produce the third brood. Thus, the mutagenicity of the anaesthetic combinations on germ cells at different stages (spermatozoa, spermatids and spermatocytes) was tested.

The F_1 (first filial generation) flies were collected for 2–3 days to ensure adequate numbers and sexual maturity. The F_1 female flies with kidney-shaped red eyes then were mated individually with three of their Basc brothers in individual vials. Twenty or more F_1 females flies were mated from each of the 30 P_1 (first parental generation) treated male flies, for a total of about 600 F_1–P_2 (first filial–second parental generation) female flies per brood (table I). The F_1–P_2 flies were removed from the vials after 5 days and their eggs allowed to hatch. Cultures were kept for 12–14 days to guarantee that male flies with semilethal mutations characterized by a longer development hatched. The F_2 (second filial generation) progeny for each brood were examined using a dissecting microscope over a 10-day period, beginning with day 1 of emergence of fly from pupa, to determine the occurrence of sex-linked recessive lethals. The absence of wild-type males indicated lethality. Only cultures with 40 or more progeny (males and females together) were included. If 40 or more progeny were present, and no wild-type male flies were observed, the culture was deemed to contain a lethal, since the chance of a type I error is less than 1 in 1000. The frequency of lethals was calculated by dividing the number of lethals found in each brood by the total number of tested X-chromosomes in each brood. The Fisher's exact test was used to compare the lethal mutation rates among the treatment groups. $P < 0.05$ was considered significant.

RESULTS

The spontaneous rate of sex-linked recessive mutations observed in the control group of male wild-type flies exposed only to air was 0.22% (table I). This value is within the normal range found by other investigators (Würgler, Sobels and Vogel, 1977). Rates of mutation for flies exposed to nitrous oxide, enflurane of isoflurane alone were 0.27%, 0.17% and 0.32%, respectively, and were not significantly different from control values (Kundomal and Baden, 1985). Neither 2% enflurane nor 2% isoflurane was mutagenic in the presence of 75% nitrous oxide (table I).

Halothane produced a dose-dependent increase in the rate of lethal mutations: 1% and 2% concentrations produced about four-fold and seven-fold increases above control, respectively (table I). A dose-dependent increase above two-fold is generally considered a positive response (Würgler, Sobels and Vogel, 1977). There was no difference in mutagenic response among the broods, indicating that all stages of germ cells were equally affected. Nitrous oxide had no effect on the mutagenicity of halothane.

DISCUSSION

Nitrous oxide has no mutagenic activity when tested alone in a variety of assays with bacteria, mammalian cells or whole animals (Baden, 1985). In particular, it is not mutagenic when tested with *Drosophila melanogaster* in the sex-linked recessive assay (Kundomal and Baden, 1985). Nitrous oxide interferes, however, with vitamin B_{12} and folate metabolism and can thereby produce several long-term toxic effects in both experimental animals and man (Nunn and Chanarin, 1985). It also is synergistic with halothane in the production of nuclear abnormalities in dividing fibroblasts (Sturrock and Nunn, 1976). Finally, it has the potential for enhancing the acute hepatotoxicity of halothane in experimental animals (Ross, Monk and Duffy, 1984). Thus, one may reasonably hypothesize that, although not itself a chemical mutagen, nitrous oxide enhances the mutagenic potential of other drugs such as halothane, enflurane and isoflurane. Results from the present study do not support such a hypothesis. This is encouraging, since nitrous oxide and volatile anaesthetics are commonly administered together to patients, and are present together in the waste anaesthetic gases which may be inhaled by operating room personnel.

The positive mutagenic response seen in the present study with halothane alone needs to be put in perspective. This finding is consistent with those from previous studies in this species performed by ourselves (Kundomal and Baden, 1985) and others (Kramers and Burm, 1979; Clements and Todd, 1981). In general, there are several toxicological implications if a chemical is found to be a mutagen (Flamm and Lorentzen, 1985). First, mutagens produce heritable changes in genetic information which usually are deleterious and may produce a variety of congenital anomalies in future generations. Second, chemicals able to bind covalently to DNA and produce mutations are often able to bind covalently to other tissue macromolecules such as proteins and lipids and produce further toxicity. Third, mutations are thought to be important first steps in the formation of cancers.

Whilst the importance of chemical mutagens is not in doubt, the best method with which to identify them remains uncertain. Since no single test is completely reliable, most authorities believe that a battery of tests should be performed and that a positive response should be seen in several before a chemical is labelled as a mutagen (Flamm and Lorentzen, 1985). On this basis, halothane cannot be regarded as a proven chemical mutagen because it is not mutagenic other than in the *Drosophila* assay. In particular, it is not mutagenic when tested under a wide variety of conditions in the Ames test using bacteria to which mammalian enzyme systems have been added (Baden et al., 1976; Waskell, 1978). It also does not induce sister chromatid exchanges, widely regarded as related to mutations, in cultered Chinese hamster ovary cells at clinical concentrations (White et al., 1979); nor does it cause mutations in cultured Chinese hamster lung fibroblast cells using the azaguanine test system (Sturrock, 1977). Finally, halothane lacks mutagenic effects when administered to rodents *in vivo* at various clinical doses (Basler and Rohrborn, 1981). In keeping with its lack of mutagenicity in mammalian test systems is its lack of carcinogenicity (Eger et al., 1978; Baden et al., 1979; Coate, Ulland and Lewis, 1979) and teratogenicity (Kennedy et al., 1976; Landsdown et al., 1976; Wharton et al., 1979) when tested *in vivo* in various bioassays with rodents. Overall, negative results in mammalian test systems and failure to enhance the mutagenic response with nitrous oxide in *Drosophila* suggest that mutation and its consequences are unlikely features of halothane toxicity in the clinical setting.

ACKNOWLEDGEMENTS

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NON-COMPETITIVE EFFECTS OF DISOPYRAMIDE AT THE NEUROMUSCULAR JUNCTION: EVIDENCE FOR ENDPLATE ION CHANNEL BLOCK

S. V. P. JONES AND I. G. MARSHALL

SUMMARY

The effects of disopyramide were studied at the neuromuscular junction in an attempt to elucidate the mechanism of its blocking action at this site. Disopyramide 5×10^{-5}–10^{-3} mol litre^{-1} produced a concentration-dependent reduction of twitch amplitude in the indirectly stimulated chick biventer cervicis preparation, but greater concentrations were required to reduce twitches elicited directly in the presence of erabutoxin-b 1 µg ml^{-1}. Equieffective twitch blocking doses of either disopyramide or tubocurarine greatly reduced agonist responses to acetylcholine and carbachol, but the reduction was less for magnesium-blocked twitches. Neostigmine antagonized tubocurarine-induced, but not disopyramide-induced, blockade of twitches. Concentration–response profiles to acetylcholine and carbachol were shifted to the right in a non-parallel fashion and the maximal response was depressed by disopyramide 5×10^{-5}–10^{-4} mol litre^{-1}. Intracellular recording studies carried out in the cut, voltage-clamped costocutaneous muscle of the garter snake showed that disopyramide 5×10^{-5}–5×10^{-4} mol litre^{-1} produced a concentration- and voltage-dependent reduction of the amplitude of neurally evoked endplate-currents (EPC) and of the time constant of decay (τ) of EPC. We conclude that disopyramide possesses a non-competitive blocking action at the neuromuscular junction, which is not reversible by anticholinesterase agents. The voltage-dependent nature of the block suggests that it is mediated via blockade of the open form of the acetylcholine-activated receptor–ion channel complex.

Disopyramide is an antiarrhythmic agent which blocks the fast inward sodium current of cardiac muscle and prolongs the duration of cardiac action potentials (Sekiya and Vaughan Williams, 1963; Kojima, 1981). In addition, the compound has been shown to have an antimuscarinic effect on the heart (Mirro et al., 1980). Nicotinic cholinoceptor blocking actions of disopyramide have been reported both at autonomic ganglia and at the skeletal muscle neuromuscular junction in *in vitro* experiments (Byrne et al., 1981; Healy, O'Shea and Massey, 1981). The antagonism towards cholinoceptor agonists was non-competitive in nature in the frog rectus abdominis muscle (Byrne et al., 1981) and the reduction of twitch responses in the indirectly stimulated rat diaphragm preparation was not reversible by anticholinesterase administration (Healy, O'Shea and Massey, 1981). On the basis of these observations it was suggested that disopyramide might interact with neuromuscular blocking agents (Healy, O'Shea and Massey, 1981).

It is known that certain agents, including local anaesthetics, barbiturates and some antibiotics, act at the neuromuscular junction by a non-competitive mechanism which can be attributed to blockade of endplate ion channels (Adams, 1976; Ruff, 1977; Fiekers et al., 1983). Such non-competitive blockade, like that reported for disopyramide, would be expected to be irreversible by

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anticholinesterases. In this study we have investigated the actions of disopyramide by twitch tension recording both in isolated preparations and *in vivo*. In addition, we have performed electrophysiological recording studies to assess the possible endplate ion channel blocking action of the compound. In these latter studies voltage clamp techniques were used to record endplate currents in response to stimulation of motor nerves. The time constant of decay of the endplate current affords a measure of underlying channel activity and hence changes in this value in the presence of drugs can be interpreted in terms of actions on the endplate channels.

Some of the results described in this paper have previously been published in abstract form (Harvey, Jones and Marshall, 1984).

MATERIALS AND METHODS

Tension recording studies

Chick biventer cervicis nerve–muscle preparation. The chick biventer cervicis muscle is a mixed muscle comprising both focally and multiply innervated fibre types. Consequently, it is possible to record both fast twitches, which arise mainly from the focally innervated fibres in response to stimulation of motor nerves, and slow contracture responses to exogenously applied agonists, from the multiply innervated fibres, hence giving a measure of postjunctional receptor responsiveness. This allows predictions to be made on the potential mechanisms of action of added pharmacological neuromuscular blocking agents.

Chicks aged 7–14 days were killed with ether and the two biventer cervicis muscles were removed and mounted in Krebs–Henseleit solution (Krebs and Henseleit, 1932) containing double glucose maintained at 32 °C and gassed with oxygen containing 5% carbon dioxide (Ginsborg and Warriner, 1960). The muscles were stimulated indirectly via the motor nerve at a frequency of 0.1 Hz with rectangular pulses of 0.2 ms duration and of a strength greater than that required to elicit a maximal twitch (generally 5–10 V). At intervals nerve stimulation was stopped and either acetylcholine 10^{-3} mol litre^{-1} or carbachol 2×10^{-5} mol litre^{-1} was added to the tissue bath to produce contractures. Acetylcholine and carbachol were allowed to remain in contact with the tissues for 30 s and 90 s, respectively, before washout.

For the construction of dose–response curves to carbachol, each preparation was exposed to three concentrations of antagonist.

For direct stimulation of the muscle, neuromuscular transmission was abolished by the irreversible snake venom toxin, erabutoxin b 1 µg ml^{-1} (Harvey and Rodger, 1978). The ring electrodes were placed around the belly of the muscle. The muscle was stimulated at 0.1 Hz for 0.2 ms at a strength greater than that required to produce maximal twitches (generally 100–150 V).

All blocking drugs were allowed to equilibrate with the tissue for 30 min before the effects of agonists or reversal agents were tested in their presence.

Tibialis anterior muscle preparation of anaesthetized rats. Male Sprague–Dawley rats (350–500 g), were anaesthetized with sodium pentobarbitone 60 mg kg^{-1} i.p. One hind limb was immobilized and the tendon of the tibialis anterior muscle was isolated and attached to a Grass FT10C force displacement transducer. The sciatic nerve was stimulated at a frequency of 0.1 Hz, as for the chick biventer cervicis muscle preparation, with rectangular pulses of 0.2 ms duration and of strength sufficient to produce maximal twitches of the tibialis anterior muscle. A polythene cannula was inserted to a jugular vein for injection of drugs. Arterial pressure was measured from the carotid artery by a Statham P23Ac pressure transducer. Artificial ventilation was applied, when required, through a tracheal cannula (1.5 ml/100 g per breath; 54 b.p.m.).

Electrophysiological recording

Microelectrode recordings were obtained from the costocutaneous nerve–muscle preparation of the North American garter snake (*Thamnophis sirtalis*). This preparation is particularly suitable for voltage clamp recording from the neuromuscular junction as it possesses large diameter fibres which aid visualization and penetration of endplates. This, coupled with compact endplates, allows good control of membrane voltage over the entire endplate region when using the two-microelectrode voltage clamp technique. In order to record evoked endplate currents (EPC) whilst avoiding muscle contraction, a cut fibre preparation was used (Fiekers et al., 1983).

The nerve–muscle preparations were dissected and the muscle fibres cut in a physiological salt solution of pH 7.1–7.2 containing (mmol litre^{-1}) NaCl 159; KCl 2.15; $CaCl_2$ 2.0; $MgCl_2$ 4.2;

HEPES 1.0). After the fibres were cut, preparations were perfused for 15 min with a high calcium (10-mmol litre^{-1}) solution in order to prevent too large a decrease in membrane potential. The mean membrane potential in the cut fibre preparation was -40 ± 1 mV ($n = 57$). The muscles were mounted in a Sylgard-coated Perspex dish and endplates were voltage clamped using glass capillary microelectrodes (resistance 2–10 MΩ). Voltage-recording electrodes were filled with potassium chloride 3 mol litre^{-1} and current-passing electrodes filled with potassium citrate 2 mol litre^{-1} and potassium sulphate 0.6 mol litre^{-1} (1:1) (Dionne and Parsons, 1981).

The nerve was stimulated through platinum electrodes at a frequency of 0.5 Hz with rectangular pulses of 0.05 ms duration and of strength sufficient to produce EPC. EPC were filtered by a 5-kHz low pass filter and recorded on magnetic tape (Racal 4DS bandwidth DC—5 kHz). The currents were amplified and digitized by a Cambridge Electronic Design 502 laboratory interface connected to a DEC PDP 11/23 computer at a digitization rate of 25 kHz. Ten to twenty EPC were collected and averaged after alignment at the middle of their rising phase. EPC decayed as a single exponential function according to the following relationship:

$$I(t) = I(0)\exp^{(-t/\tau)}$$

where $I(t)$ is the current amplitude at time t after the peak, $I(0)$ is the peak current amplitude and τ is the decay time constant. The value τ was calculated by computer from the reciprocal of the slope of the least squares regression line fitted to the semilogarithmic plot of amplitude between 5% and 95% of the peak against time. EPC with a 10–90% rise time greater than 0.4 ms were discarded and only those with a voltage deviation of less than 1% of the driving force (holding potential − reversal potential) accepted. Experiments were carried out at room temperature (20–22 °C).

Drug solutions were perfused through the tissue bath for 5 min by peristaltic pump, ensuring a complete change of solution. A further 10 min was allowed before measurements were made.

Drugs and solutions

The drugs used were acetylcholine chloride, carbachol chloride, tubocurarine chloride (Sigma), pentobarbitone sodium (May & Baker), neostigmine methylsulphate (Roche), disopyramide phosphate (Searle or Roussel), erabutoxin b (a gift from Professor N. Tamiya, Tohoku University, Japan, to Dr A. L. Harvey). Drugs were dissolved in 0.9% saline or physiological salt solutions as used in the experiment.

Statistics

Except where stated in the text, the results are expressed as the means ± standard error of measurements from at least five different preparations. Differences between means were tested by Student's non-paired t test, t values with $P < 0.05$ being regarded as significant.

RESULTS

Disopyramide 5×10^{-5}–10^{-4} mol litre^{-1} produced a concentration-dependent reduction of the amplitude of indirectly elicited twitches of the chick biventer cervicis muscle preparation. As shown in figure 1, the relationship between concentration and percentage inhibition of directly excited twitches was particularly steep in the range disopyramide 5–8×10^{-4} mol litre^{-1}. In directly stimulated, irreversible toxin-treated preparations the concentrations of disopyramide previously shown to produce block of indirectly stimulated twitches caused a 30–40% increase in the size of directly-elicited twitches. Reductions of responses to direct stimulation were produced only by concentrations of disopyramide which were

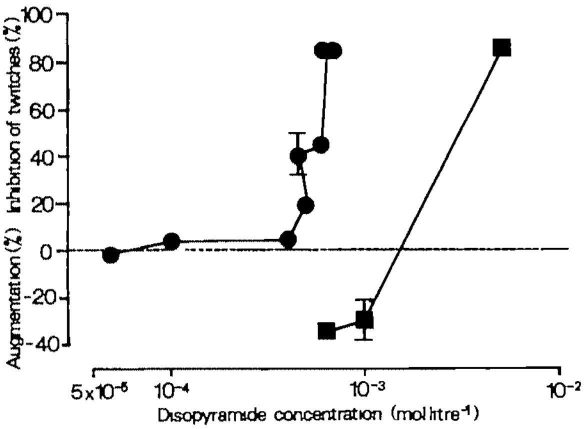

FIG. 1. Effects of disopyramide on directly (■) and indirectly (●) elicited twitches of the chick biventer cervicis muscle. Results are expressed as % inhibition or % augmentation (negative inhibition). Each point represents the mean ± SEM of six experiments. Error bars are omitted when smaller than the symbols. Note the more potent effect of disopyramide on indirectly elicited twitches than on directly elicited twitches.

greater than those necessary to abolish completely the indirectly elicited twitches (fig. 1).

As the main site of action of disopyramide appeared to be at the neuromuscular junction, the compound was compared, in indirectly stimulated preparations, with the mainly postjunctionally active receptor blocking agent, tubocurarine, and with the mainly prejunctionally active magnesium ion. All three substances reduced indirectly elicited twitches but, at approximately equal degrees of twitch blockade (around 20, 50 and 80%), disopyramide, tubocurarine and magnesium produced markedly different effects on contracture responses to added agonists (fig. 2). For example, at 20% block of twitches tubocurarine 2.5×10^{-6} mol litre^{-1} and disopyramide 5×10^{-4} mol litre^{-1} produced a greater depression of acetylcholine (57 ± 5% and 89 ± 5%, respectively, $n = 6$) and carbachol contractures (100 ± 0% and 100 ± 0%, respectively, $n = 6$), than did magnesium 3×10^{-3} mol litre^{-1}, which produced only 12 ± 6% ($n = 6$) depression of acetylcholine contractures and 46 ± 8% ($n = 6$) reduction of carbachol contractures. Similar effects were seen

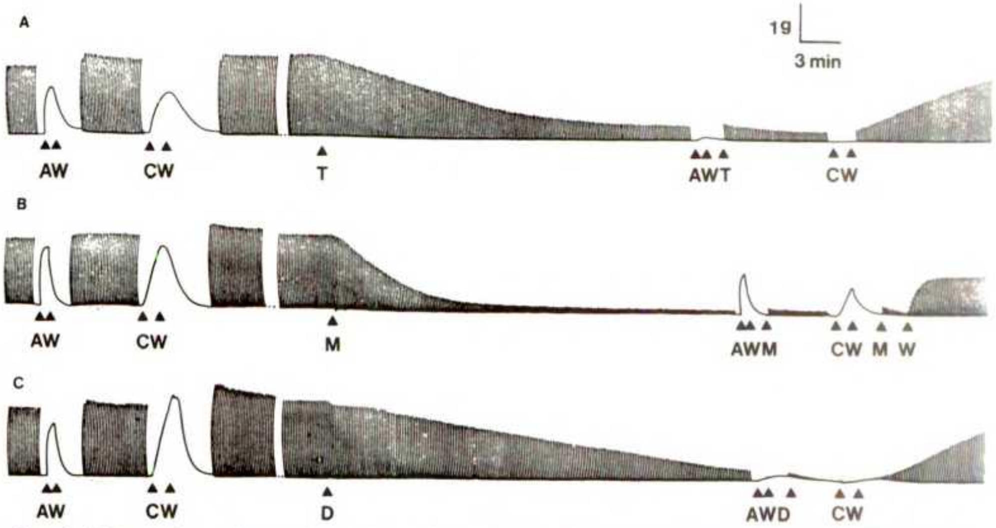

FIG. 2. Effects of: A, tubocurarine 4.5×10^{-6} mol litre^{-1} (T); B, magnesium ion 1.2×10^{-2} mol litre^{-1} (M); and C, disopyramide 7×10^{-4} mol litre^{-1} (D) on indirectly elicited twitches and on responses to acetylcholine 10^{-3} mol litre^{-1} (A) and carbachol 10^{-5} mol litre^{-1} (C) in the isolated chick biventer cervicis muscle. W represents washout of the tissue bath with fresh Krebs solution. Note the lesser effect of magnesium than either tubocurarine or disopyramide on agonist responses.

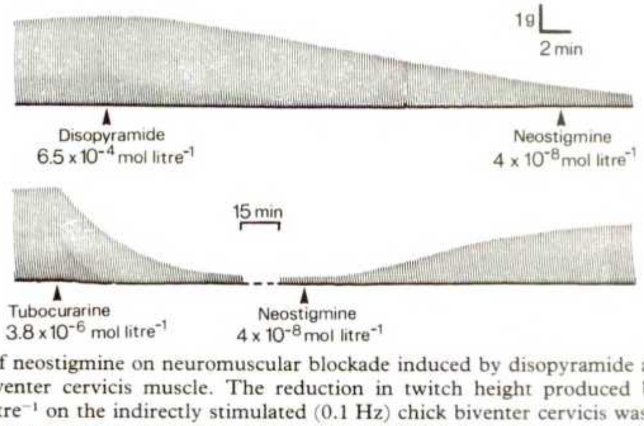

FIG. 3. Effects of neostigmine on neuromuscular blockade induced by disopyramide and tubocurarine in the chick biventer cervicis muscle. The reduction in twitch height produced by disopyramide 6.5×10^{-4} mol litre^{-1} on the indirectly stimulated (0.1 Hz) chick biventer cervicis was not reversed by neostigmine 4×10^{-8} mol litre^{-1} (upper trace). The twitch block induced by tubocurarine 3.8×10^{-6} mol litre^{-1} was reversed by neostigmine 4×10^{-8} mol litre^{-1} (lower trace).

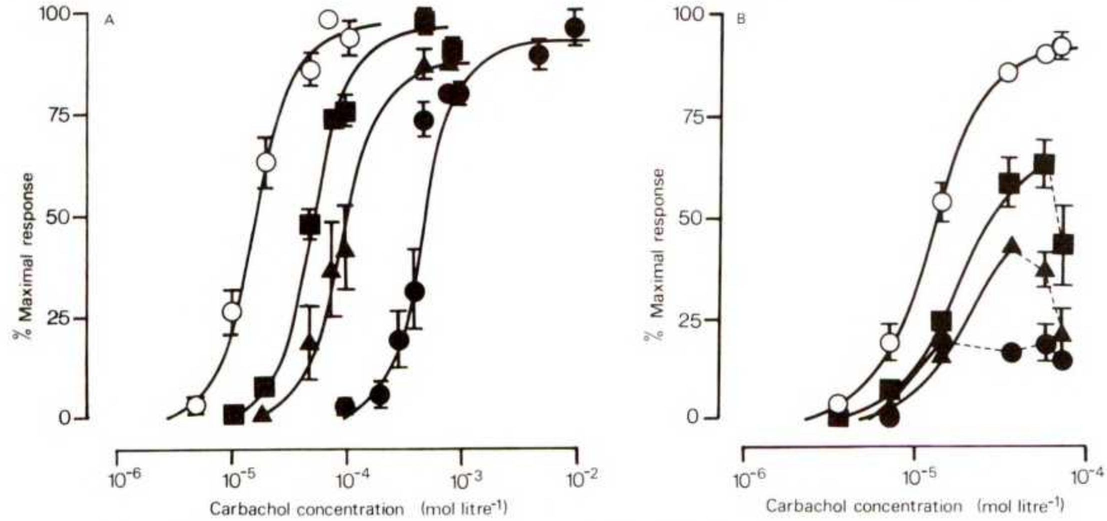

FIG. 4. Concentration–response curves to carbachol in the absence and presence of tubocurarine and disopyramide. A: The control curve to carbachol (○) is moved progressively to the right in a parallel fashion by increasing concentrations of tubocurarine: 10^{-6} mol $litre^{-1}$ (■), 5×10^{-6} mol $litre^{-1}$ (▲) and 10^{-5} mol $litre^{-1}$ (●). B: the control curve to carbachol is moved to the right in a non-parallel manner and the maximal response is greatly depressed by increasing concentrations of disopyramide: 5×10^{-5} mol $litre^{-1}$ (■), 8×10^{-5} mol $litre^{-1}$ (▲) and 10^{-4} mol $litre^{-1}$ (●). In both A and B each point is the mean ± SEM of six experiments.

at 50% and 80% inhibition of twitch heights. Thus the actions of tubocurarine and disopyramide on agonist responses were somewhat similar, but were both different from the actions of magnesium.

Nevertheless, a major difference between tubocurarine and disopyramide was revealed by attempts to reverse the neuromuscular blockade with an anticholinesterase. Thus in six preparations neostigmine 4×10^{-8} mol $litre^{-1}$ reversed the blockade produced by tubocurarine 4×10^{-6} mol $litre^{-1}$ from $83 \pm 4\%$ to $24 \pm 2\%$ twitch block. However, neostigmine 4×10^{-8} mol $litre^{-1}$ had no reversing effect on the twitch blockade caused by disopyramide 6.5×10^{-4} mol $litre^{-1}$ (fig. 3).

In order to obtain more information on the type of antagonism exerted by disopyramide, its effects were compared with those of tubocurarine on dose–response curves constructed for carbachol (fig. 4). As expected, tubocurarine produced parallel shifts of concentration–response curves to carbachol (fig. 4A). The pA_2 value of tubocurarine against carbachol was calculated from Arunlakshana and Schild plots to be 6.2 ± 0.2—a value similar to that previously obtained in this preparation (Gandiha, Green and Marshall, 1972). In contrast, in the presence of disopyramide 5×10^{-5}–10^{-4} mol $litre^{-1}$, concentration–response curves for carbachol (fig. 4B) were shifted to the right in a non-parallel fashion and the maximal response was depressed.

In vitro *intracellular recording experiments*

Endplate currents were recorded over a range of membrane potentials from −50 to −130 mV. Hyperpolarization of the endplate membrane leads to a linear increase in amplitude of EPC as a result of the increased driving force for ionic flow (membrane potential − acetylcholine channel reversal potential). Hyperpolarization also results in an exponential increase in EPC time constant (τ) as a result of increasingly greater electrical hindrance to the closing of the channel at greater membrane potentials (Magleby and Stevens, 1972). Thus (as seen in figure 6) semilogarithmic plots of τ *v.* membrane potential produce straight lines in the absence of blocking drugs.

Disopyramide 5×10^{-5}–5×10^{-4} mol $litre^{-1}$ produced a concentration-dependent decrease in the peak amplitude of EPC (fig. 5). Examination of the EPC records shown in figure 5 shows that the drug not only reduced peak EPC amplitude, but also shortened the time to peak (that is, the rise time of the EPC, not the rate of the rise) and the time constant of decay.

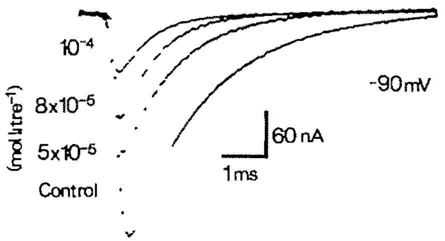

FIG. 5. The effects of increasing concentrations of disopyramide (5×10^{-5}–10^{-4} mol litre^{-1} on averaged endplate currents (EPC) from the cut snake costocutaneous muscle preparation. Note that the increasing concentrations of disopyramide produce a progressive decrease in EPC amplitude and decay time, with a concomitant reduction in rise time. Records represent the superimposed averages of approximately 20 EPC recorded in the absence and presence of the drug.

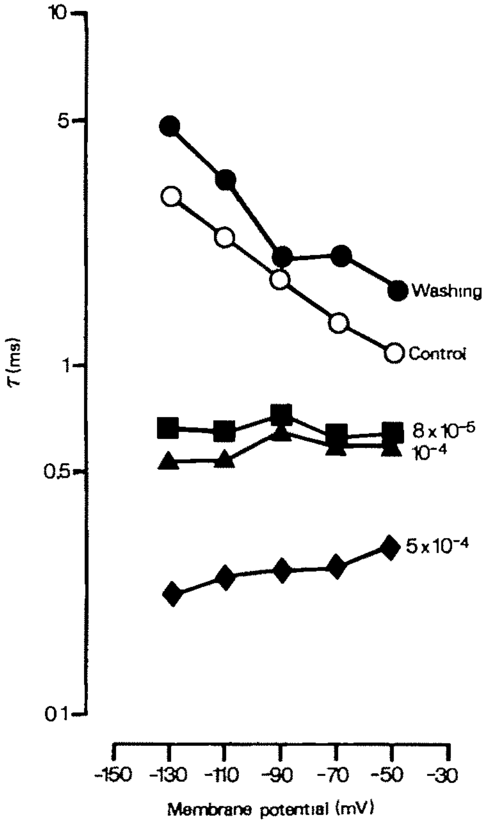

FIG. 6. Semilogarithmic plot of the time constant of decay (τ) *v.* membrane potential from a representative experiment performed on the cut snake costocutaneous muscle. In the absence of drug (○) τ is voltage-dependent. Increasing concentrations of disopyramide (8×10^{-5} mol litre^{-1} (■), 10^{-4} mol litre^{-1} (▲) and 5×10^{-4} mol litre^{-1} (◆)) produce a progressive flattening and then reversal of the normal voltage-dependency. Thus the percentage reduction of τ is greatest at hyperpolarized membrane potentials. Note the reversal of the effects of disopyramide by washing (●).

The effects of disopyramide on the time constant of decay (τ) are shown in figure 6. Here it can be seen that increasing concentrations of disopyramide lead to a progressive decrease in τ, the percentage reduction being greater at hyperpolarized membrane potentials. It can also be seen from figure 6 that, at the highest concentration of disopyramide used (5×10^{-4} mol litre^{-1}), the normal voltage-dependence of τ, represented by the slope of the τ *v.* membrane potential plot, is reversed. These results are consistent with an action of disopyramide at the level of the endplate ion channel.

In several experiments in which the reversibility of the effects of disopyramide was tested by washing, EPC amplitude and time course were shown to return to control values

In vivo *tension recording experiments*

In the anaesthetized rat tibialis anterior muscle–sciatic nerve preparation, disopyramide alone in doses up to 5 mg kg^{-1} produced no effect on twitch tension. In greater doses it produced an increase in twitch height. For example, in one experiment, doses of 30 and 40 mg kg^{-1} produced 20 and 37% augmentation, respectively. However, when the safety factor in neuromuscular transmission was reduced by tubocurarine such that indirectly elicited twitches were depressed by about 50%, large doses of disopyramide (10–40 mg kg^{-1}) produced a significant but only very transient (1–2 min duration) deepening of the blockade of muscle twitches (table I). This was accompanied by a marked degree of bradycardia.

DISCUSSION

Our initial results obtained from the isolated chick biventer cervicis muscle preparation simply

TABLE I. *Effects of disopyramide on the tibialis anterior nerve–muscle preparation of the anaesthetized rat. Twitches had been previously reduced to 50% of control by tubocurarine. Mean ±standard error of five experiments.* **Significantly different from control* ($P < 0.05$)

Disopyramide concentration (mg kg^{-1})	Reduction of twitch height (%)
Control	0±0%
5	−0.4±0.7%
10	3.8±0.4%*
20	8.2±1.6%*
30	16.0±2.7%*
40	22.5±2.6%*

confirm and extend those of Byrne and colleagues (1981) and Healy, O'Shea and Massey (1981). Thus the experiments in directly and indirectly stimulated preparations show that very high concentrations of disopyramide are required to affect muscle contractions and that, therefore, the main effect of the drug in the preparation is at the neuromuscular junction. The augmentation of twitch height seen under certain recording conditions is suggestive of disopyramide blocking potassium channels in electrically excitable membranes. The comparison of disopyramide with tubocurarine and magnesium indicated that the predominant site of action was postjunctional, but the lack of reversibility of disopyramide by neostigmine pointed to a basic difference between the actions of disopyramide and tubocurarine. This was confirmed by the finding that disopyramide affected dose–response curves to exogenous agonists in a manner inconsistent with competitive postjunctional blockade of acetylcholine receptors.

Given the above results, and taking into account the high concentrations of disopyramide required to produce them, coupled with its known local anaesthetic activity (Baines et al., 1976), we were able to predict that the compound acted at the neuromuscular junction by blocking the open form of the endplate ion channels. This prediction was borne out by the finding that disopyramide reduced the time constant of decay of EPC in a concentration- and voltage-dependent manner. Such behaviour is generally interpreted in terms of the sequential model of endplate ion channel block (Adams, 1975; Ruff, 1977; Adler, Albuquerque and Lebeda, 1978), as follows:

$$\underset{\text{closed}}{\mathrm{ACh}+\mathrm{R}\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}\mathrm{AChR}}\underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}}\underset{\text{open}}{\mathrm{AChR}^{*}+\mathrm{D}}\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}}\underset{\text{blocked}}{\mathrm{AChR}^{*}\,\mathrm{D}}$$

where ACh is acetylcholine, R the acetylcholine receptor, D the channel blocking drug, k_1, k_2 and k_3 are the forward rate constants and k_{-1}, k_{-2} and k_{-3} the backward rate constants for the reaction.

In this scheme disopyramide would interact, not as a competitive receptor blocker with R, but rather with the open form of the acetylcholine receptor–ion channel complex, AChR*. Such an interaction explains the non-competitive, anticholinesterase-resistant block. Thus, increasing the concentration of acetylcholine, rather than overcoming the blockade, will tend to result in more open channels; this will result in a greater opportunity for disopyramide to effect blockade. One apparent anomaly in this explanation is that, if the drug does not interact with R, then the model predicts that AChR and AChR* will be formed—that is, the endplate channels will open normally in the presence of the drug before being blocked. Thus the peak of the current should not be reduced, but its time course should be shortened as a result of the blockade of the open channels. In fact, it is a common observation that channel blocking drugs reduce EPC amplitude. This is because the release of acetylcholine is not instantaneous from all the release sites. As a result of this temporal dispersion of release, some quanta which are released fractions of a millisecond after the first to be released, will encounter receptors of which the associated ion channels have already been opened, and therefore may be blocked by the drug. These quanta will not be able to act and therefore the peak current will be reduced. A further clue to this comes from the observation that EPC rise time is reduced, that is the channel block is curtailing the action of slowly released quanta and hence reducing the rise time in a concentration-dependent manner. When release is instantaneous, as during a miniature endplate current which results from the release of a single quantum of acetylcholine, channel blockade alone should not reduce amplitude.

Many endplate channel blocking drugs produce EPC with two decay phases, one faster and one slower than control decay (Adams, 1975; Beam, 1976; Adler, Albuquerque and Lebeda, 1978; Fiekers, Marshall and Parsons, 1979; Henderson et al., 1986). This is because, with certain drugs, k_{-3} is appreciably faster than k_{-2}. Thus the channels can reopen and pass further current. If k_{-3} is relatively slow, then only single exponential decays are discernible. The single exponential decay measured with disopyramide is thus indicative of a slow unblocking rate constant. The kinetic aspects of the channel blocking action of disopyramide will be dealt with in a subsequent paper.

Finally, we move to the significance of channel blockade *in vivo*. It is clear that the effects of disopyramide on neuromuscular transmission in the intact animal were modest, very transient and possibly related to a decrease in muscle blood perfusion as a result of the cardiovascular changes. We have observed similar extremely weak and transient actions of the channel blocking antibiotics clindamycin and lincomycin in anaesthetized cats (Marshall, Houston and Henderson unpublished observations). We believe that the reason for this may be in the pharmacokinetic handling of the drugs in the biophase. This can be illustrated by reference to the buffered diffusion model proposed by Hull, English and Sibbald (1980) and reviewed by Hull (1982). According to this model, a drug such as tubocurarine which interacts with the receptor, or recognition site (albeit for only a very brief period (Colquhoun and Sakmann, 1985)), can interact many times before it is removed from the biophase by diffusion. This is because, once the drug dissociates from the receptor the receptor is free for further association. In contrast, the ion channel is free for association only when it is opened by acetylcholine. Thus, in the absence of nerve stimulation and hence acetylcholine release, apart from any non-specific binding, the channel blocking drug will be free to diffuse away from its site of action. However, during rapid nerve stimulation, such as during voluntary activity, the chances of channel blockade producing significant effects on transmission should be increased.

Overall, we conclude that under normal circumstances the neuromuscular blocking action of disopyramide alone is unlikely to be of major importance, but that, if it is observed, the blockade is likely to be non-competitive in nature and hence irreversible by the administration of anticholinesterase. As with any agent that reduces the safety margin of neuromuscular transmission, the chances of its action becoming noticeable will be greatly enhanced when neuromuscular transmission is compromised, either by other concomitantly used drugs, or by neuromuscular disease.

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INTERACTION OF ADRENALINE WITH NEOSTIGMINE AND TUBOCURARINE AT THE SKELETAL NEUROMUSCULAR JUNCTION

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SUMMARY

The effects of neostigmine, and of neostigmine with adrenaline, on the response of the rat isolated hemidiaphragm to stimulation of the phrenic nerve are reported. Neostigmine augmented the response: a maximum augmentation occurred at a concentration of 6.4×10^{-7} mol litre^{-1}. At greater concentrations of neostigmine the response was reduced. Adrenaline in the absence of neostigmine produced no significant change in the contraction response. However, in the presence of neostigmine further augmentation occurred and achieved a maximum in the presence of adrenaline 3.2×10^{-7}–1.3×10^{-6} mol litre^{-1}. Adrenaline 4.0×10^{-8}–1.3×10^{-6} mol litre^{-1} combined with neostigmine 4.0×10^{-8}–6.4×10^{-7} mol litre^{-1} reversed tubocurarine-induced neuromuscular blockade more effectively than neostigmine alone ($P < 0.001$). Adrenaline appeared to enhance the antagonistic effect of neostigmine by increasing acetylcholine release and by enhancing the response at the post-junctional acetylcholine receptor.

The inhibition of cholinesterase by neostigmine may not be the only factor effecting the antagonism of neuromuscular blockade, as neostigmine has been shown to exert a direct action on skeletal muscle similar to that of acetylcholine (Churchill-Davidson and Christie, 1959). Blaber and Bowman (1963) also attributed the effect of neostigmine to a secondary action on the concentration of choline, and postulated that acetylcholine is released in greater amounts per impulse following an action of neostigmine on pre-junctional sites. This enhanced release of acetylcholine is augmented further by a decrease in the hydrolysis of acetylcholine.

Sometimes, the administration of neostigmine fails to restore neuromuscular transmission completely (Hunter, 1956), or the restoration is transient and paralysis recurs. Residual curarization is not uncommon, but is difficult to assess (Lennmarken and Lõfström, 1984).

The present investigation was based on the hypothesis that activity at adrenoceptors at the neuromuscular junction influences the antagonism of non-depolarizing neuromuscular blockade by neostigmine; that neostigmine-resistant curarization and recurarization might be explained on the basis of changes in catecholamine concentrations.

Several authors have described a facilitatory action of adrenaline on neuromuscular transmission in its ability to increase the augmentation of twitch response and repetitive firing produced by anticholinesterase drugs and depolarizing drugs such as decamethonium and suxamethonium (Bülbring and Burn, 1942; Bülbring, 1946; Burn and Hutcheon, 1949; Paton and Zaimis, 1950; Blaber and Bowman, 1963; Bowman and Raper, 1966). The facilitatory action of adrenaline might be explained by an anticholinesterase-like action (Burn, 1945), but this has been considered to be too weak to account for such an effect (Benson, 1948; Benson and Meek, 1949).

Catecholamine concentrations may be high during anaesthesia (Jaattela et al., 1975); however,

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after anaesthesia, they decrease. It has been shown that plasma catecholamine concentrations in man may reach approximately 5.0×10^{-8} mol litre^{-1} (Jaattela et al., 1975)—a value which falls within the range of concentrations studied in this investigation.

Several factors that cause stimulation of the sympathetic nervous system are associated with trauma; these include pain, fear, haemorrhage and tissue damage (Walker et al., 1959). A similar effect is exerted by different anaesthetic procedures (Price, 1957; Black et al., 1969) and by surgical intervention (Nikki et al., 1972).

The effectiveness and persistence of the antagonism of tubocurarine-induced neuromuscular blockade by neostigmine could, therefore, be influenced by the concentration of catecholamine (probably adrenaline) to which the neuromuscular junction is also exposed. Thus, at the end of anaesthesia, when catecholamine concentrations may be high, adequate antagonism of tubocurarine-induced neuromuscular blockade by neostigmine may be obtained. Shortly after anaesthesia, when catecholamine concentrations decrease, the degree of reversal may become inadequate.

MATERIALS AND METHODS

Response of the diaphragm to electrical stimulation via the phrenic nerve

The phrenic nerve and a wedge of diaphragm from adult male Sprague–Dawley rats (weight range 300–400 g) were dissected (Bülbring, 1946) and mounted in Krebs solution at 37 °C bubbled with 95% oxygen and 5% carbon dioxide. The diaphragm was stimulated via the phrenic nerve using single supramaximal (rectangular waveform) impulses at 0.1 Hz with a pulse duration of 0.2 ms. The contractions of the muscle were sensed with a force-displacement transducer and recorded with a pen recording system (Grass Model 7 Polygraph).

Drugs introduced to the organ bath remained in contact with the preparation for 3 min, unless otherwise stated; the preparation was then washed for 12 min with four changes of Krebs solution. The effect of each concentration of drug was measured at 3 min and expressed as a percentage change from the control response in the absence of drug. Log concentration–effect curves were plotted for each drug. Drug concentrations (mol litre^{-1}) refer to final bath concentration. The composition of the Krebs solution was (mmol litre^{-1}): NaCl 119; KCl 4.7; $CaCl_2$ 2.5, $MgSO_4$ 1.2, NaH_2PO_4 0.9, $NaHCO_3$ 25.0 and glucose 11.1.

Measurement of cholinesterase inhibition by drugs

The cholinesterase activity of homogenates of rat phrenic nerve–diaphragm preparations was assayed using the method developed by Ellman and colleagues (1961). Enzyme activity was measured photometrically by following the increase in yellow colour produced by the interaction of thiocholine with the dithiobis-nitrobenzoate ion (DTNB).

The endplate region of the diaphragm was dissected from Sprague–Dawley rats weighing 350–500 g, by removing a strip of muscle some 4–5 mm wide across the wedge of diaphragm at the point of entry of the phrenic nerve termination. The strip of muscle was weighed, chopped and homogenized in phosphate buffer (0.1 mol litre^{-1}, pH 8.0) on ice (20 mg of tissue per 1 ml of phosphate buffer). For the assays, 0.4 ml of homogenate was incubated for 3 min at 37 °C with 0.02 ml of substrate (acetyl thiocholine 5×10^{-4} mol litre^{-1} and 0.1 ml DTNB reagent in phosphate buffer 2.6 ml). For drug inhibition studies, appropriate concentrations in phosphate buffer were included in the reaction mixture. The initial volume of phosphate buffer, 2.6 ml, was reduced appropriately to keep the final volume constant. Change in absorbance was measured against a blank at 412 nm.

Retrograde venous injection of acetylcholine

The technique was based on that of Burgen, Dickens and Zatman (1949), which has also been used by Paterson (1965) and Harris and Leach (1965).

The diaphragm, right phrenic nerve, thoracic inferior vena cava and hepatic vein were dissected from male Sprague–Dawley rats (150–300 g) and placed in cold Krebs solution gassed with 95% oxygen and 5% carbon dioxide. The abdominal inferior vena cava was tied just below the diaphragm. The veins draining the left hemidiaphragm and the crura were tied and these muscles were removed. The right phrenic vein was cannulated with a polythene cannula having a deadspace of 0.2 ml. The preparation was mounted in Krebs solution at 37 °C bubbled with 95% oxygen and 5% carbon dioxide. The diaphragm was stimulated via the phrenic nerve using supramaximal rectangular waveform pulses at 0.1 Hz with a pulse duration of 0.2 ms. The contraction responses of the preparation were sensed with a force–displacement transducer and recorded with a pen recording system (Grass 7 Polygraph).

Electrical stimulation was stopped for 1 min and acetylcholine solution 0.15 ml was injected rapidly to the right phrenic vein. The procedure was repeated at 3-min intervals. A concentration–response relationship for acetylcholine in the range 10^{-6}–10^{-2} mol litre^{-1} was determined for each preparation, and repeated at the conclusion of each investigation. The fluid in the bath was exchanged after each series of injections.

Drugs were added to the organ bath to allow a contact time of 3 min before the injection of acetylcholine. The preparation was washed for 12 min after each investigation with four exchanges of Krebs solution.

Bioassay of acetylcholine released during stimulation of the isolated phrenic nerve–diaphragm preparation

Bioassay. The method used was that described by Vapaatalo, Linden and Parantainen (1976). The stomach of an adult male golden hamster (100–150 g) was dissected and the pouch was opened and cut into a strip 6–8 cm long. This was attached by one end to a tissue holder, placed in an empty 50-ml jacketed organ bath and superfused with a modified Krebs solution (mmol litre^{-1}): NaCl 118.0; KCl 4.7; $CaCl_2$, $2H_2O$ 2.5; $MgSO_4$ $7H_2O$ 1.17; KH_2PO_4 1.2; $NaHCO_3$ 25.0; glucose 11.2.

The Krebs solution was bubbled in a reservoir with 95% oxygen and 5% carbon dioxide and delivered via a warming coil to superfuse the strip at a rate of 10 ml min^{-1}. The preparation was allowed to relax for 2 h. Solutions to be assayed were injected to the superfusion cannula in 0.1-ml volumes; the final dilution of drug was made in Krebs solution. Contractions of the preparation were sensed with an isotonic transducer loaded at 0.5–0.7 g and recorded on a flat-bed pen recorder.

Acetylcholine release. The rat isolated phrenic nerve–diaphragm preparation was set up in a small organ bath in 8 ml of Krebs solution at 37 °C gassed with 95% oxygen and 5% carbon dioxide. The phrenic nerve was stimulated through bipolar platinum electrodes with pulses of 0.2 ms pulse width, at supramaximal voltage, at various frequencies, at a constant train length of 12000 impulses. At the end of each period of stimulation 0.1-ml samples of Krebs solution were removed from the bath and assayed on the hamster stomach strip. For basal recovery of contractile substance, no attempt was made to preserve acetylcholine with an anticholinesterase since this would have interfered with the investigation of the effects of neostigmine. A randomized Latin Square design was used for the assay.

RESULTS

Response of the rat phrenic nerve–diaphragm to (+)-tubocurarine and to neostigmine (fig. 1)

A progressive inhibition of the twitch response of the diaphragm occurred with increasing concentrations of tubocurarine from 1.6×10^{-7} to 2×10^{-5} mol litre^{-1}.

Neostigmine augmented the twitch response. Maximum augmentation was attained at 6.4×10^{-7} mol litre^{-1}, after which the response declined with increasing concentration.

The relation between the concentration of neostigmine and the degree of reversal of tubocurarine-induced neuromuscular blockade was also investigated. Concentrations of neostigmine 4.0×10^{-8}–6.4×10^{-7} mol litre^{-1} progressively reversed the block present after 6 min contact with tubocurarine 2.6×10^{-6} mol litre^{-1} ($P < 0.001$ at neostigmine 6.4×10^{-7} mol litre^{-1}).

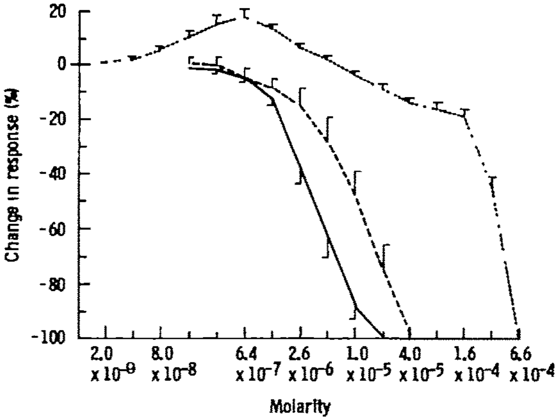

FIG. 1. Log concentration–effect curves for (+)-tubocurarine and neostigmine on the rat isolated phrenic nerve–diaphragm: percent change in twitch response to electrical stimulation of the phrenic nerve (0.1 Hz) produced by 3-min periods of exposure to various molar concentrations of the drugs. —— = (+)-Tubocurarine alone ($n = 11$); ... - neostigmine alone ($n = 7$); — — = (+)-tubocurarine in the presence of neostigmine 6.4×10^{-7} mol litre^{-1} ($n = 4$). Vertical bars represent SEM.

Reversal of blockade decreased at high concentrations of neostigmine.

Effect of adrenaline. In the presence of neostigmine 6.4×10^{-7} mol litre^{-1} (the concentration which produced maximal augmentation), the response was further augmented by adrenaline ($P < 0.001$), the maximum effect being produced by adrenaline 3.2×10^{-7} and 1.3×10^{-6} mol litre^{-1} (fig. 2A).

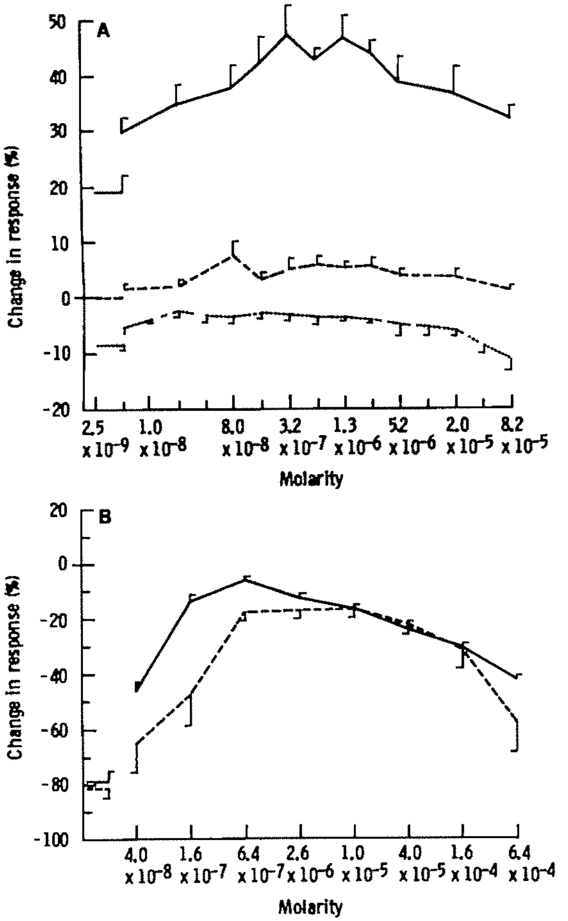

FIG. 2. Log concentration–effect curves for adrenaline neostigmine and (+)-tubocurarine on the rat isolated phrenic nerve–diaphragm: percent change in twitch response to electrical stimulation of the phrenic nerve (0.1 Hz) produced by 3-min periods of exposure to various molar concentrations of the drugs. A: Effect of adrenaline in the presence of neostigmine 2×10^{-8} mol litre^{-1} (---); 6.4×10^{-7} mol litre^{-1} (——) and 1.6×10^{-4} mol litre^{-1} (....) ($n = 5$). The horizontal bars on the left indicate the effects of those concentrations of neostigmine in the absence of adrenaline. B: Effect of neostigmine on the degree of blockade produced by (+)-tubocurarine 2.6×10^{-6} mol litre^{-1} in the absence (---) and in the presence (——) of adrenaline 1.3×10^{-6} mol litre^{-1} ($n = 5$). The horizontal bars on the left indicate the effect of (+)-tubocurarine 2.6×10^{-6} mol litre^{-1} alone for each group of experiments.

Effect of adrenaline on the antagonism by neostigmine of a tubocurarine blockade

The antagonism by various concentrations of neostigmine of the blockade of twitch response induced by tubocurarine 2.6×10^{-6} mol litre^{-1} was investigated in the presence of adrenaline. Adrenaline 1.3×10^{-6} mol litre^{-1} (a concentration shown to produce maximum augmentation of the neostigmine effect) and neostigmine 4.0×10^{-8}–6.4×10^{-7} mol litre^{-1} antagonized the tubocurarine blockade more effectively than the same concentrations of neostigmine alone (fig. 2B). For example, an 80% block of a response by tubocurarine after 6 min, reduced to 50% block by neostigmine 1.6×10^{-7} mol litre^{-1} ($P < 0.01$, $n = 5$), was further decreased to a 15% block in the presence of adrenaline 1.3×10^{-6} mol litre^{-1} ($P < 0.001, n = 5$). Concentrations of neostigmine greater than 6.4×10^{-7} mol litre^{-1} in the presence of adrenaline 1.3×10^{-6} mol litre^{-1}, whilst causing a significant reduction of the tubocurarine-induced blockade ($P < 0.001$), did not significantly alter the degree of antagonism obtained with the use of neostigmine alone.

Cholinesterase inhibition

Neostigmine 6.4×10^{-7} mol litre^{-1} inhibited the cholinesterase activity of the endplate region of the diaphragm by $91.7 \pm 0.9\%$ ($n = 5$). The inhibition was not significantly greater $95.2 \pm 1.2\%$ ($n = 5$) when the concentration of neostigmine was increased to 1.3×10^{-6} mol litre^{-1}.

When adrenaline 3.2×10^{-7} mol litre^{-1} was combined with neostigmine 6.4×10^{-7} mol litre^{-1}, the inhibition was $95.8 \pm 1.1\%$ ($n = 5$). A combination of adrenaline 1.3×10^{-6} and neostigmine 6.4×10^{-7} mol litre^{-1} gave an inhibition of $95.4 \pm 0.9\%$ ($n = 5$).

Response of the rat phrenic nerve–diaphragm to retrograde venous injection of acetylcholine

The response to retrograde injection of acetylcholine, over a concentration range from 10^{-6} to 10^{-2} mol litre^{-1} increased with increasing concentration of acetylcholine up to a maximum response achieved at 10^{-3} mol litre^{-1} ($n = 8$). A log concentration–response curve for acetylcholine was plotted for each diaphragm preparation at the beginning of each investigation.

Adrenaline 2×10^{-8} mol litre^{-1} in the presence of neostigmine 6.4×10^{-7} mol litre^{-1} increased ($P < 0.001$) the response to acetylcholine 10^{-5} mol litre^{-1}. The higher concentrations of adrenaline 1.3×10^{-6} and 2.0×10^{-5} mol litre^{-1} effected no significant change. In the absence of neostigmine, adrenaline did not change significantly the response to acetylcholine.

The effects of neostigmine and adrenaline on the release of acetylcholine by the rat isolated diaphragm in response to 12000 shocks via the phrenic nerve at various frequencies (fig. 3)

Acetylcholine recovered in 0.1-ml aliquots from the Krebs solution bathing the diaphragm stimulated at 5.0 Hz for 40 min produced a response in the hamster stomach strip.

The concentration (mean 3.8±0.4% of the maximum response) was approximately equivalent to acetylcholine 10^{-11} g/ml of standard solution. As the frequency of stimulation was increased an increased amount of contractile substance was recovered. At a stimulation rate of 40 Hz for 5 min, the response of the stomach strip was 14.2±0.3% of maximum (equivalent to acetylcholine 3.0×10^{-10} g ml^{-1}, approximately). There was a reduction in the quantity of contractile substance recovered at the higher frequency of 80 Hz.

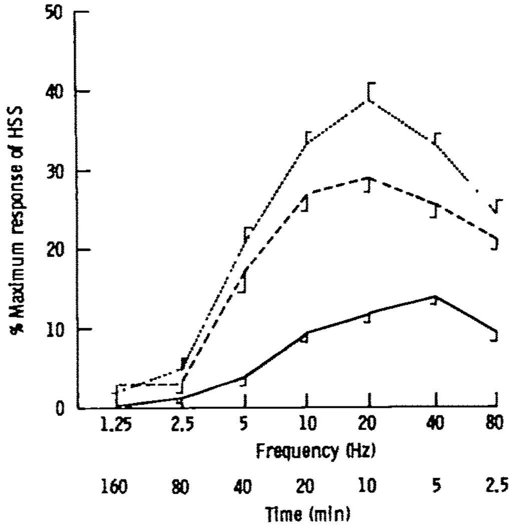

FIG. 3. The effect of neostigmine 6.4×10^{-7} mol litre^{-1} alone (—) or with adrenaline 1.3×10^{-6} mol litre^{-1} (....) on the recovery of acetylcholine from the rat isolated phrenic nerve–diaphragm preparations ($n = 5$). —— = Recovery in the absence of adrenaline or neostigmine. The contraction response of the hamster stomach strip (HSS) as a percentage of the maximum response to acetylcholine is plotted against frequency of stimulation of phrenic nerve on a log scale for a fixed number of stimuli (12000) at each frequency from 1.25 to 80 Hz.

A significant increase in the quantity of contractile substance recovered at stimulation frequencies of 5–20 Hz ($P < 0.001$, $n = 5$) resulted from the addition of neostigmine 6.4×10^{-7} mol litre^{-1} to the bath fluid. The maximum quantity recovered was approximately equivalent to acetylcholine 8.0×10^{-10} g ml^{-1}. At the frequencies of 40 and 80 Hz, less was recovered than at 5–20 Hz.

The combination of adrenaline 1.3×10^{-6} and neostigmine 6.4×10^{-7} mol litre^{-1} further increased the recovery of contractile substance. This increase over neostigmine alone was significant ($P < 0.02, n = 5$) at stimulus frequencies of 10, 20 and 40 Hz.

Characterization of contractile substance. Separate investigations were performed to characterize the substance recovered from the rat diaphragm preparation during phrenic nerve stimulation. Inclusion of atropine 5.0×10^{-7} mol litre^{-1} or hyoscine 10^{-7} mol litre^{-1} in the fluid superfusing the hamster stomach strip abolished the ability of standard acetylcholine solutions and of aliquots of Krebs recovered from the baths of stimulated diaphragms to contract the stomach strip.

When diaphragms stimulated through the phrenic nerve were exposed to tetrodotoxin 10^{-7} mol litre^{-1} or to hemicholinium 10^{-5} mol litre^{-1}, aliquots of Krebs removed from the bath did not contract the stomach strip.

The stomach strip did not contract when exposed to solutions of acetylcholine, or to aliquots of Krebs solution from the baths of stimulated diaphragms, which had been mixed with sodium hydroxide 2 mol litre^{-1} and allowed to stand at room temperature for 5 min.

DISCUSSION

The phenomenon of augmentation by adrenaline of neostigmine-induced reversal of neuromuscular blockade produced by tubocurarine was reproduced in the isolated phrenic nerve diaphragm–preparation; the efficacy of the optimum concentration of neostigmine 6.4×10^{-7} mol litre^{-1} was enhanced by adrenaline 1.3×10^{-6} mol litre^{-1}. This enhancement was shown not to be the result of further cholinesterase inhibition by adrenaline;

the combination of neostigmine and adrenaline had no more inhibitory effect on cholinesterase activity in the diaphragm than did neostigmine alone.

Measurements were made of the presynaptic release of acetylcholine and of the postsynaptic sensitivity to acetylcholine. It was clear that neostigmine increased the recovery of a substance that had the characteristics of acetylcholine. Adrenaline further augmented this neostigmine-induced increase in acetylcholine recovery.

Thus it appears that adrenaline enhanced the effect of neostigmine by increasing the acetylcholine concentration—by delaying its destruction or by increasing its release. This is in agreement with the findings of Bowman and Raper (1966), Bowman and Nott (1969) and Kuba (1970).

The sensitivity of the muscle to injected acetylcholine was not significantly enhanced by neostigmine alone, but was enhanced when adrenaline was present, showing that there is also a postsynaptic component to the augmentation produced by adrenaline.

Thus it could be summarized that the enhanced effect of neostigmine and adrenaline in reversing tubocurarine-induced neuromuscular blockade is mediated prejunctionally and postjunctionally.

Since the finding that adrenaline increases the acetylcholine-induced contracture of the isolated diaphragm of the kitten, and that it exerts a biphasic effect on the potentiation of the twitch response to indirect stimulation by prostigmine (Dale and Gaddum, 1930; Bülbring and Burn, 1942) the effects of catecholamines upon the neuromuscular junction and the muscle tissue have been extensively investigated. The neuromuscular or muscular effects of the catecholamines in intact animals have often been attributed to vascular effects; frequently, no effect could be found in isolated preparations. Bowman and Raper (1965) demonstrated that many of the effects of catecholamines upon the neuromuscular actions of tubocurarine and anticholinesterases were independent of arterial pressure and flow.

It has been shown that both adrenaline and noradrenaline increase anticholinesterase-produced twitch potentiation and repetitive firing (Blaber and Bowman, 1963; Bowman and Raper, 1965; Bowman and Raper, 1967). The catecholamines exert a biphasic action on tubocurarine-induced blockade, the synergistic effect being generally delayed. Bowman and Raper (1966, 1967) concluded that the facilitatory actions of adrenaline and noradrenaline were attributable to nerve terminal effects associated with α-adrenoceptor activity, but that the inhibitory effects were related to postsynaptic β-adrenoceptor activity.

Work by Hidaka and Kuriyama (1969) demonstrated that noradrenaline acts mainly on presynaptic nerve terminals to increase the release of transmitter, and that adrenaline acts mainly at the postsynaptic membrane to increase the sensitivity to acetylcholine, thereby enhancing the amplitude of excitatory junction potentials. Kuba (1970), and Kuba and Tomita (1971) agreed with these findings and found that isoprenaline acts on the postsynaptic membrane to enhance the input resistance.

Taken together, we believe that the results of our investigations reported here and those of others described above, support a hypothesis that changes in catecholamine concentrations during anaesthesia and surgery could have an influence on neostigmine-resistant curarization and recurarization. During anaesthesia and surgery when adrenaline concentrations are likely to be high, adequate antagonism of competitive neuromuscular blockade may be obtained with neostigmine; however, as the concentration of adrenaline decreases after surgery, the degree of reversal may become inadequate.

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PRESENT STATE OF EXTRADURAL AND INTRATHECAL OPIOID ANALGESIA IN SWEDEN

A Nationwide Follow-up Survey

N. RAWAL, S. ARNÉR, L. L. GUSTAFSSON AND R. ALLVIN

SUMMARY

A nationwide follow-up survey was undertaken to study the use of extradural and intrathecal opioids in the management of pain, to estimate the incidence of delayed ventilatory depression and to study post-injection surveillance routines. A questionnaire was sent to all 93 anaesthetic departments in Sweden; 96% responded. The major indication for using extradural opioids was the treatment of postoperative, traumatic and cancer pain. During 1984 over 14000 patients received extradural, and over 1100 patients intrathecal, opioids. Morphine was the predominant opioid for extradural administration and was used in 96% of patients. Extradural opioid analgesia constitutes about 25% of all extradural blocks performed in Sweden. Pruritus and urinary retention were considered as minor problems; however, the risk was considerably higher after intrathecal morphine. The incidence of delayed ventilatory depression was about 1:1100 (0.09%) following extradural morphine and 1:275 (0.36%) following intrathecal morphine. Risk factors for delayed ventilatory depression are discussed. Administration of extradural morphine for postoperative pain relief in patients undergoing major surgery is considered a high benefit–low risk technique by most Swedish anaesthetists. The results of the present nationwide survey suggests that, following extradural morphine, surveillance of patients for more than 12 h appears unnecessary.

Within a relatively short time of its introduction, the technique of injecting opioid drugs to the extradural or intrathecal spaces has become well-established in the management of acute and chronic pain. A number of controlled studies have shown the superiority of extradural opioids over alternative techniques in the treatment of severe postoperative pain (Lanz et al., 1982; Shulman et al., 1984; Rawal et al., 1984). However, the technique is not completely free of risk. The major limiting factor to a more widespread use of the technique is the need for postoperative surveillance in a recovery room or intensive care unit because of the potentially dangerous occurrence of delayed ventilatory depression, the reported incidence of which is about 0.3–0.9% following extradural, and 4–7% following intrathecal, morphine (Cousins and Mather, 1984). Although important administratively and economically, the optimal duration of surveillance after the administration of intraspinal opioids is unclear from the literature. In a nationwide survey (in 1981) related to the use of extradural and intrathecal opioids in the management of pain, the incidence of ventilatory depression was reported and risk factors associated with this complication identified (Gustafsson, Schildt and Jacobsen, 1982). Although clinical knowledge about this modality of treatment has increased greatly, many questions remain unanswered and a follow-up study was considered appropriate.

The aims of the present nationwide survey were:

(1) To study the clinical acceptance and extent of

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use of extradural and intrathecal opioids in the management of pain in Sweden.

(2) To estimate the incidence of ventilatory depression following the administration of intraspinal opioids and identify possible risk factors.

(3) To attempt to make extradural and intrathecal opioid administration safer by providing clearer guidelines for postoperative surveillance.

PATIENTS, MATERIALS AND METHODS

A 13-page questionnaire was sent, with the support of the Swedish Society of Anaesthesiologists, to all 93 anaesthetic departments in Sweden. One of the authors (LG) was involved with the 1981 questionnaire (Gustafsson, Schildt and Jacobsen, 1982). The anaesthetist most actively involved in the use of extradural or intrathecal opioids in each department was requested to furnish the relevant information. The questions were identical for extradural and intrathecal opioid administration and were presented as "yes" or "no" alternatives to simplify the answers and their evaluation. The questions were answered by crossing the appropriate boxes. The following questions were asked:

1 and 2. Do you use extradural or intrathecal opioids for providing pain relief?

3. If yes, for which type of pain? Postoperative, traumatic, labour, perioperative and/or cancer pain?

4. How long have you used the technique? Less than 1 year, 1–2 years, 2–4 years or 4–6 years?

5. How many patients have you treated with extradural/intrathecal opioids during 1984? The usage of morphine, pethidine or other opioids was requested for each type of pain mentioned under question 3.

6. Do you use extradural/intrathecal opioids for postoperative pain relief after any of the following types of surgery? Thoracic, upper abdominal, lower abdominal, hip, knee, Caesarean section or other types of surgery.

The anaesthetists were asked to give their opinion regarding the type of surgery in which extradural or intrathecal opioids, or both, were especially useful. They were also asked if they administered extradural opioids at the lumbar or thoracic level to treat pain originating in the thoracic segments.

One of the major objectives of the study was to get as much information as possible about ventilatory depression following the extradural and intrathecal administration of opioid drugs. The questionnaire was designed with this aim. To facilitate evaluation it was formulated as follows:

7. *Ventilatory depression*

During 1984 have you observed ventilatory depression following the administration of extradural/intrathecal opioids which required treatment with naloxone?

What are your criteria for defining ventilatory depression? Specify the total number of patients, and the number of patients in whom ventilatory depression was noted within 1 h of the extradural/intrathecal administration of opioid and the number of patients in whom ventilatory depression occurred more than 1 h after the extradural administration of an opioid.

The number of hours between the last injection of an opioid and the occurrence of ventilatory depression was also sought. If ventilatory depression was noted the anaesthetists were also requested to give the following information:

Name and dose of opiate given in the extradural or subarachnoid space, age of patient, ASA risk group, premedication, if surgery was performed under regional blockade or under general anaesthesia using i.v. opioids, use of supplementary analgesics or sedatives, or both, in the postoperative period. The anaesthetists were also asked whether treatment with naloxone was successful or whether any further measures were necessary. In addition they were asked if they nursed their patients with the head of the bed raised to prevent delayed ventilatory depression.

8 and 9. *Urinary retention and pruritus*

The anaesthetists were asked if, in their opinion, urinary retention or pruritus associated with the extradural/intrathecal administration of opioid drugs was a major problem, a minor problem, or whether these adverse effects did not occur.

10. Information was also requested about other adverse effects, including neurological complications.

11. Finally, the anaesthetists were asked about their surveillance routines following the extradural/intrathecal opioid injection. They were also asked their opinion about the optimal duration of surveillance; they were asked if patients should be nursed:

a) In a general ward.

b) In a postoperative department or ICU for at least 12 h.

c) In a postoperative department or ICU for at least 24 h.

Reminders were sent to the chairmen of those departments which did not respond. A second reminder was sent to the remaining non-responders. For additional information one of the authors (NR) contacted by telephone most of the anaesthetists responsible for the extradural/intrathecal administration of opioids at their departments. A nurse anaesthetist (RA) compiled data and visited the anaesthetic departments to go through their records if data related to delayed ventilatory depression were considered inadequate.

The questionnaire also included questions related to use of extradural and intrathecal opioids for long term management of chronic malignant and nonmalignant pain. The results will be presented separately.

RESULTS

Eighty-nine (96%) of the 93 anaesthetic departments in Sweden responded to the questionnaire. Of these 82 (92%) used extradural opioids and 23 (26%) intrathecal opioids in the management of pain. All 23 departments that used intrathecal opioids also used extradural opioids. The reason for not using extradural opioids in the remaining departments was either the lack of resources for surveillance after intraspinal opioid injection or that the departments treated only children.

As can be seen from figure 1, the major indications for the technique were the treatment of postoperative, traumatic and cancer pain. The percentage of anaesthetic departments using extradural opioids to manage these were 95%, 76% and 82%, respectively. Perioperative pain was treated in 34% of the departments; labour pain in only 6%.

The number of departments using extradural opioids was 1 (4) for less than 1 year, 7 (7) for 1–2 years, 36 (9) for 2–4 years and 38 (3) for 4–6 years; the figures in parentheses represent the number of departments using intrathecal opioids. During 1984 a total of 14 139–14 313 patients were treated with extradural opioids and a total of 1103–1108 patients received intrathecal opioids. The figures are somewhat approximate since some anaesthetists could not give the exact number of patients treated. Morphine was by far the predominant opioid in use for extradural and intrathecal administration. Thus during 1984 morphine was used for 96.1%, pethidine for 2.7% and buprenorphine in the remaining 1.2% patients (table I). The usual dose of morphine for extradural administration was 4 mg and for intrathecal administration 0.2–0.8 mg.

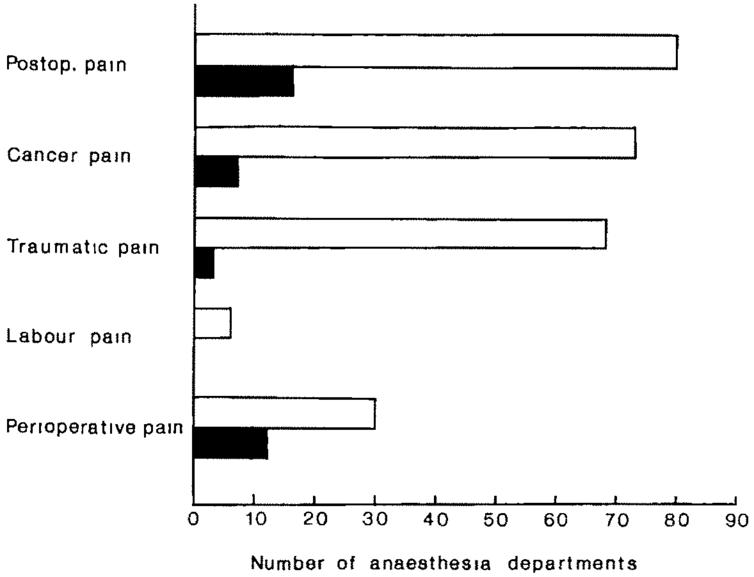

FIG. 1. Indications for the use of extradural and intrathecal opioids in Sweden.

TABLE I. *Total number of patients treated with extradural opioids during 1984 in Sweden. Figures in parentheses represent number of patients treated with intrathecal opioids during the same period*

	Morphine		Pethidine		Buprenorphine	
Postoperative pain	10791–10818	(254–256)	269–273	(5)	134	(—)
Perioperative pain	1222–1236	(822–824)	—	(—)	2	(—)
Cancer pain	737–765	(17–18)	60	(—)	24	(1)
Traumatic pain	643–662	(9–10)	55	(—)	17	(—)
Labour pain	267	(—)	—	(—)	—	(—)
Total	13660–13748	(1102–1108)	384–388	(5)	177	(1)

TABLE II. *The extent of the use of extradural and intrathecal opioids for treating pain following different types of surgery. *Thoracic surgery on a regular basis is performed in only six anaesthetic departments*

	Extradural opioids		Intrathecal opioids	
Site of surgery	Number of departments	%	Number of departments	%
Thoracic*	22	(27.7)	1	(1.1)
Upper abdominal	74	(83.1)	1	(1.1)
Lower abdominal	75	(84.3)	4	(4.5)
Hip	49	(55)	11	(12.4)
Knee	39	(43.8)	6	(6.7)
Caesarean section	12	(13.5)	—	(—)

The total numbers of patients receiving extradural and intrathecal morphine for postoperative, traumatic, labour, perioperative and cancer pain are shown in table I. Table II shows the number of departments using extradural and intrathecal opioids for postoperative pain after different types of surgery. In addition to the types of surgery shown in table II, extradural opioids were also administered for transurethral, vascular, traumatic, transvesical and pelvic surgery. In a few patients the technique was also used for non-surgical conditions such as myocardial infarction, postherpetic neuralgia and low back pain. In addition, intrathecal morphine was used for analgesia after transurethral surgery.

Patients undergoing upper abdominal, thoracic and hip surgery were considered most suitable for extradural opioid analgesia by a majority of the anaesthetic department. For intrathecal opioid analgesia, orthopaedic and urological surgery were considered the most useful indications. Most anaesthetists also commented that the technique was particularly suitable for providing postoperative pain relief for high-risk patients.

For pain of thoracic origin, the number of anaesthetic departments using the lumbar site of injection of extradural opioids was 25 (28%), a similar number (28%) used the thoracic site of injection, while 22 (25%) departments did not have any special preference. The remaining departments did not have any experience. It should be noted that thoracic surgery is performed on a regular basis in only six departments in Sweden. Nearly all anaesthetists who preferred the thoracic site did so because they used local anaesthetics extradurally during surgery and later used opioids via the extradural catheter for postoperative analgesia. According to some anaesthetists, the choice of lumbar or thoracic site of injection also depended on the competence of the anaesthetist. In one department the extradural catheters were introduced through lumbar segments to the desired thoracic level.

If intrathecal opioids were used, they were always administered as a single injection at the time of intrathecal block with local anaesthetic agent for surgery. The only exception was patients who received intrathecal opioids through a catheter for the long-term treatment of the pain of malignancy. The reason given for not using intrathecal opioids as extensively as extradural opioids was the higher risk of occurrence of ventilatory depression. Six anaesthetists had personal experience of this complication; the remainder believed it to be a potential problem on the basis of reports in the literature.

Adverse effects

Ventilatory depression. During 1984, 14 departments observed ventilatory depression which required treatment with naloxone following the extradural administration of an opioid. Two of the 21 departments using intrathecal opioids noted this complication. A total of 19 patients developed ventilatory depression which was believed to be related to the use of extradural opioids. In all cases the opioid used was morphine. Six patients (0.04%) showed signs of ventilatory depression within 1 h of the injection of the morphine. In the remaining 13 patients ventilatory depression was noted between 3 and 12 h following the extradural injection of morphine. Thus the incidence of delayed ventilatory depression was about 1 in 1100 (0.09%). The data on patients who developed delayed ventilatory depression after extradural morphine are shown in table III. Ten of these 13 patients were at least 65 years old and they all belonged to ASA risk III–IV. All patients had general anaesthesia in addition to an extradural block with local anaesthetic for surgery. Many patients also had a narcotic premedication as well as a local anaesthetic agent, plus an opioid administered via the extradural catheter for postoperative pain relief (table III). Five patients had received two to four injections of extradural morphine. As can be seen in table III, patients were also given supplementary parenteral analgesics or sedatives, or both, in the postoperative period. In 11 patients the site of the extradural injection was lumbar; in the remaining two patients it was thoracic. All patients were nursed in either a recovery room or ICU. In all cases a low ventilatory rate (less than 10 b.p.m.) was the main or only sign of ventilatory depression. All patients who had early or delayed ventilatory depression responded to naloxone; none required intubation of the trachea. A single injection i.v. of naloxone successfully reversed ventilatory depression in nine patients; in the remaining four patients the naloxone had to be repeated. In one of these four patients, four injections of naloxone 0.02 mg were given during a 4-h period. Another patient required three injections of naloxone (0.4-mg, 0.08-mg and 0.12-mg doses) over 3 h. A third patient was given three injections of naloxone 0.08 mg over 1 h. The fourth patient

TABLE III. *Delayed ventilatory depression following extradural morphine. Patient data.* **1-RD interval = time between last injection of extradural morphine and occurrence of ventilatory depression. Ox. = Oxicone (narcotic); Hyo. = hyoscine; Peth. = pethidine; Dixyr. = dixyrazine (sedative and antiemetic); Mo. = morphine. NA = Data not available*

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Patient No.	Age (yr)	ASA risk group	Premedication	General anaesth.	Extradural morphine dose (mg)	Parent. analgesic/ sedative	Extradural local anaesth.	1-RD* interval (h)	Remarks
1	75	III–IV	Ox. + Hyo.	+	2	No	Yes	3	
2	24	III	Ox. + Hyo.	+	4 × 3	Yes	Yes (several)	6	Grossly obese patient. Morphine 12 mg extradurally over 18 h.
3	57	II–III	Peth. + Dixyr.	+	4 × 4	No	Yes (several)	4.5	Duration of surgery (cystectomy) 12 h.
4	20	I	NA	+	3	No	Yes	5	Vent. rate 3–5 b.p.m. during sleep. Normal ventilation when awake.
5	70	III–IV	Ox. + Hyo.	+	3	No	No	4	
6	67	III–IV	Dilaudid	+	3	Yes	Yes	4	
7	76	III–IV	Dilaudid	+	3	Yes	Yes	4	
8	72	III–IV	Diazepam	+	6 × 2	No	No	10	
9	70	III–IV	Mo. + Hyo.	+	4	No	No	5	
10	72	III–IV	Mo. + Hyo.	+	4	No	No	12	
11	74	III–IV	—	+	3	No	Yes	10	
12	70	III–IV	—	+	4 × 2	No	No	4	
13	67	III–IV	Lorazepam	–	4 × 2	Yes	No	7	Obese patient with chronic ventilatory insufficiency following accidental gas inhalation.

TABLE IV. *Adverse effects following extradural and intrathecal morphine. *Many patients had the bladder catheterized as a result of the nature of surgery*

	Major problem		Minor problem		Does not occur	
	Extradural opioids	Intrathecal opioids	Extradural opioids	Intrathecal opioids	Extradural opioids	Intrathecal opioids
Urinary retention*	13%	38%	81%	50%	6%	12%
Pruritus	5%	14%	88%	53%	7%	33%

required two injections of naloxone 0.08 mg to achieve adequate antagonism of ventilatory depression. In the opinion of anaesthetists from seven departments, nursing the patients in the headup position after the extradural or intrathecal injection of an opioid, did not prevent delayed ventilatory depression. The remaining anaethetists had no experience of this, since the patients were normally nursed supine.

Four patients (0.36%) developed delayed ventilatory depression following intrathecal morphine. This occurred 7–9 h after injection and was successfully reversed by naloxone. Three of these patients received morphine 0.3 mg and one patient intrathecal morphine 0.75 mg. One patient was classified as risk II–III and the remaining three risk III–IV. All the four patients were premedicated with pethidine and promethazine. Intrathecal morphine was injected at the same time as the local anaesthetic agent to provide peri- and postoperative analgesia. None of these patients received general anaesthesia or concomitant parenteral sedatives or opioids.

Many anaesthetists commented that, when ventilatory depression occurred it was usually not unexpected, since extradural opioids were predominantly used in high-risk patients. In their opinion, the advantages outweighed the potential danger of ventilatory depression.

Urinary retention and pruritus. The data for the incidence of urinary retention and pruritus was incomplete. However, there was a clear difference between intrathecal and extradural opioids (table IV). Following intrathecal morphine, urinary retention was considered a major problem by 38% of anaesthetists and pruritus by 14%; the corresponding figures for extradural morphine were 13% (urinary retention) and 5% (pruritus). However, it should be noted that many patients had a catheterized bladder because of the nature of surgery, thus making assessment of urinary retention difficult.

Neurological complications. Neurological complications were noted in five patients receiving extradural and one patient receiving intrathecal opioids. Transient paraesthesiae were noted in three of the patients; one of these patients also had transient motor paresis. Catatonia was seen in two patients; this was transient in one patient and lasted 2 h in the other. In one patient there was prolonged urinary incontinence, paresis and paraesthesiae in the lower extremities. The case was reported to the Swedish Health Board, which ruled out extradural morphine as the cause.

Postoperative surveillance

The answers to the question related to postoperative surveillance varied considerably. Twenty-nine departments (33%) observed their patients in the postoperative department or ICU for 12–24 h after intraspinal opioids, 36 departments (40%) carried out such surveillance for up to 12 h while 16 (18%) did not provide any special surveillance and believed that these patients could be nursed in a general surgical ward. Many anaesthetists commented that young and otherwise healthy patients could be nursed in a general ward while old, high-risk patients should be nursed in the postoperative (recovery) area or ICU. In the opinion of these anaesthetists patients in the latter category often require surveillance even if intraspinal opioids are not used.

DISCUSSION

The present survey shows that the technique of administering opioids extradurally and intrathecally is well-established in Sweden. Almost all anaesthetic departments have been using the technique for the past 2–6 years. The survey also shows that, during the past 3 years, the use of extradural opioids has increased considerably, while the use of intrathecal opioids has decreased. The number of patients treated with extradural opioids during 1984 was much larger than the total number of patients treated with the technique during the 2-year period up to 1981 (Gustafsson, Schildt and Jacobsen, 1982). It may be of interest to note that about 60000 extradural blocks and 36000 intrathecal blocks are performed annually in Sweden (B. Hallén and M. Puke, personal communication). Thus extradural opioid analgesia constitutes about 25% of all extradural blocks performed in Sweden.

The major indication for the technique is the treatment of postoperative pain, traumatic pain and cancer pain. Management of postoperative pain in high-risk patients undergoing major surgery was considered as the most suitable indication for the technique by a majority of the anaesthetists. Extradural opioids were used more frequently and by more anaesthetists than intrathecal opioids. The number of patients receiving extradural opioids was about 14 times greater than those receiving intrathecal opioids.

In Sweden morphine is still the drug of choice for extradural and intrathecal administration. Nearly all anaesthetists prefer to use morphine rather than other opioids. The indications for choosing the intrathecal or the extradural route for opioid administration were different. Intrathecal morphine was used as a single injection combined with a local anaesthetic agent to provide peri- and postoperative pain relief mainly following orthopaedic surgery. In contrast, extradural morphine was used mainly to provide only postoperative pain relief following major abdominal, thoracic and orthopaedic surgery, and was usually given on demand through an extradural catheter.

The adverse effects of extradural morphine are well-known. The commonest problems are pruritus and urinary retention and the most dangerous is delayed ventilatory depression (Gustafsson, Schildt and Jacobsen, 1982; Rawal et al., 1983; Cousins and Mather, 1984; Rawal and Wattwil, 1984; Stenseth, Sellevald and Breivik, 1985). Although exact figures are difficult to determine in a survey of this nature, the incidence of pruritus was generally low after extradural morphine—although considerably higher after intrathecal morphine. Since the bladder of the majority of patients was catheterized because of the nature of surgery, the incidence of urinary retention was difficult to assess. However, 13% of anaesthetists considered this as a major problem when morphine was given extradurally and 39% when morphine was administered intrathecally. Similar findings have been reported by others; a rather high incidence of non-ventilatory complications was noted even when very low doses of intrathecal morphine (0.1 mg) were used (Glass et al., 1985).

The reason given by most anaesthetists for not using intrathecal opioids as often as extradural opioids was the fear of increasing the risk of adverse effects. This appears justified. The present study has shown that the risk of delayed ventilatory depression is four times higher if morphine is given intrathecally rather than extradurally. Reducing the dose of intrathecal morphine to less than 0.5 mg has been shown to give adequate analgesia without ventilatory depression (Bengtsson, Löfström and Merits, 1983; Glass et al., 1985). However, three patients in the present survey developed delayed ventilatory depression after intrathecal morphine 0.3 mg. It should be noted that none of these patients received supplementary analgesics or sedatives in the postoperative period. This suggests that even low doses of intrathecal morphine are not free from risk.

The results of our survey show that old age, poor general condition and the residual effects of general anaesthesia are the most important risk factors for delayed ventilatory depression. More than half the patients treated for delayed ventilatory depression had also received supplementary local anaesthetics extradurally. This suggests that the combination of local anaesthetics and opioids extradurally may be an additional risk factor (table III). The majority of patients were older than 65 years. One of the younger patients was a grossly obese 24-yr-old male classified as ASA risk III-IV. One patient was a healthy normal 20-yr-old male who, after extradural administration of morphine 4 mg, had ventilatory frequency of 3–5 b.p.m. when he slept, but normal ventilatory frequency when he was awake. The present study supports the findings of the previous survey, that large doses of extradural morphine (more than 4 mg) and concomitant parenteral analgesics or sedatives, or both, may be responsible for increasing the risk of delayed ventilatory depression. A single injection of naloxone reversed ventilatory depression in nine patients; in the remaining four patients the naloxone had to be repeated. However, late recurrence of ventilatory depression was not seen in any of these patients. It has been reported that ventilatory depression can be prevented by nursing the patients in the head-up position following intraspinal opioid administration (McCaughey and Graham, 1982). Although no figures were provided, because of the rarity of the complication, none of the anaesthetists believed that ventilatory depression could be prevented by this procedure.

This study suggests that anaesthetists in Sweden have taken known risk factors into consideration in selecting appropriate patients thereby reducing the incidence of delayed ventilatory depression from the 0.25–0.4% reported in the previous survey (Gustafsson, Schildt and Jacobsen, 1982) to 0.09%. Since the technique was considered particularly useful in old, high-risk patients undergoing major surgery, it was believed that the advantages of the technique such as potent segmental analgesia, early ambulation and shorter hospitalization (Rawal et al., 1982; Rawal et al., 1984) outweighed the rare risk of delayed ventilatory depression. It should be noted that many anaesthetists commented that providing postoperative intraspinal opioid analgesia in this category of patients was a calculated risk and that if ventilatory depression occurred it was usually not unexpected.

It has been speculated that the lipophilicity of the opioid administered extradurally or intrathecally may have an important role in preventing the occurrence of delayed ventilatory depression. Using radioactively labelled morphine and pethidine to study the CNS distribution in animals it has been postulated that hydrophilic morphine persists longer in the spinal cord than lipophilic pethidine (Gustafsson et al., 1985). Thus this complication is believed to be most common with hydrophilic morphine and rare with lipophilic opioids like fentanyl (Cousins and Mather, 1984). However, ventilatory depression has been reported with lipophilic opioids such as buprenorphine (Christensen and Andersen, 1982; Knape, 1986), pethidine (Albright, 1983), heroin (Watson et al., 1984), alfentanil (Chauvin et al., 1983) and even fentanyl (Parker et al., 1985). Therefore, none of the presently available opioids is completely safe, and morphine still appears to be the commonest opioid administered extradurally or intrathecally. However, the post-injection surveillance routines vary considerably. This is also reflected in the results of the present study. Eighteen percent of anaesthetists considered the technique safe enough to nurse their patients in a general surgical ward. Forty percent of anaesthetists recommended 12 h while 33% recommended 24 h of surveillance at a high dependency unit.

The requirement for surveillance and the duration of surveillance after intraspinal opioid administration have important administrative and economic implications. These are major factors in restricting the technique mainly to patients who require surveillance in a postoperative recovery ward or an ICU environment as a result of the nature of surgery or their poor general condition, or both. Therefore, the requirement of prolonged surveillance also limits the more widespread use of intraspinal opioid analgesia. In the present study none of the approximately 14000 patients treated with extradural morphine during 1984 showed any evidence of ventilatory depression after 12 h of extradural morphine injection. In the previous survey comprising about 6000–9000 patients 22 patients developed ventilatory depression. In none of these did the complication occur after 12 h of extradural opioid administration (Gustafsson, Schildt and Jacobsen, 1982). In another study 10 out of 1085 patients (0.9%) receiving extradural morphine showed evidence of delayed ventilatory depression. In none of these patients did ventilatory depression occur 12 h after injection of extradural morphine (Stenseth, Sellevald and Breivik, 1985). Based on the results of these large surveys we believe that, when therapeutic doses of morphine (4 mg or less) are administered extradurally, postinjection surveillance of more than 12 h appears unnecessary. Recommendations for other opioids cannot be made from the results of the present study.

In conclusion, nearly all the anaesthetic departments in Sweden use extradural opioids in the treatment of pain. The use has increased greatly since 1981. In spite of possible theoretical disadvantages the predominant opioid is still morphine and the commonest route of administration is extradural rather than intrathecal. The commonest indication is treatment of postoperative pain in high-risk patients undergoing major abdominal, thoracic or orthopaedic surgery. When extradural morphine is administered to this category of patients, one patient in about 1100 can be expected to develop delayed ventilatory depression. The risk can be reduced by avoiding known risk factors. However, based on the results of the present survey it can be postulated that the extradural administration of morphine is a high benefit–low risk technique. The risk of ventilatory depression is about four times higher when morphine is administered intrathecally. Therefore, all patients irrespective of age or type of surgery, who receive extradural or intrathecal opioids should be observed for signs of delayed ventilatory depression. However, on the basis of our nationwide survey, surveillance for more than 12 h appears unnecessary.

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HAEMODYNAMIC EFFECTS FOLLOWING SURGICAL RELEASE OF INCREASED INTRA-ABDOMINAL PRESSURE

M. P. SHELLY, A. A. ROBINSON, J. W. HESFORD AND G. R. PARK

SUMMARY

The haemodynamic indices of three patients, who developed abdominal tamponade as a result of intra-abdominal bleeding following liver transplantation, were measured on four occasions as the increased intra-abdominal pressure was released. Hypotension followed the release of the tamponade in all patients and was the result of a decrease in systemic vascular resistance. This was treated with vasoconstrictors; the response to various agents was monitored. Treatment of hypotension following release of abdominal tamponade by volume replacement alone may be inappropriate and may lead to over-transfusion; adrenaline may be the treatment of choice. Intensive haemodynamic monitoring is advisable.

Although the haemodynamic effects of increased intra-abdominal pressure have been documented, the changes which immediately follow decompression have not. We report the haemodynamic changes observed on four occasions immediately before and after the release of abdominal tamponade resulting from intra-abdominal bleeding. Measurements made during the release of the tamponade in the first patient indicated that rapid blood transfusion at the time of decompression was inappropriate. Observations were, therefore, made in a more controlled manner in two further patients on three subsequent occasions, when more personnel were available to assist with the more frequent and intensive monitoring of cardiovascular function.

CASE REPORTS

Patient 1

The first patient was a 35-year-old man who underwent orthotopic liver transplantation for hepatic failure secondary to sclerosing cholangitis. After surgery he continued to bleed from intra-abdominal sites and required massive blood transfusion; blood was lost from abdominal drains and he developed a tense distended abdomen. His coagulation screen was slightly abnormal in spite of the infusion of fresh frozen plasma and platelet concentrate, but there was no clinical evidence of a significant coagulation disorder—such as bleeding from the nose, mouth, pharnyx or the sites of venous and arterial cannulation.

Eight hours after his liver transplant operation, laparotomy was undertaken to evacuate intra-abdominal clot and to achieve haemostasis. During the re-exploration, cardiovascular variables were measured: heart rate (HR) was taken from the electrocardiogram, mean arterial pressure (MAP) was measured via an indwelling radial artery catheter and mean right atrial pressure (RAP), mean pulmonary artery pressure (MPAP) and pulmonary capillary wedge pressure (PCWP) were measured using a pulmonary artery catheter (Edwards Laboratories) positioned immediately before surgery. Cardiac output (CO) was measured by a thermodilution technique and values were calculated for systemic (SVR) and pulmonary (PVR) vascular resistances.

On opening the peritoneal cavity, approximately 6 litre of blood and clot was removed. No arterial bleeding points were found to account for the haemorrhage; there was a general ooze from many intra-abdominal sites. Intraoperative hypotension was treated with blood transfusion; however, since calculation showed the SVR to be

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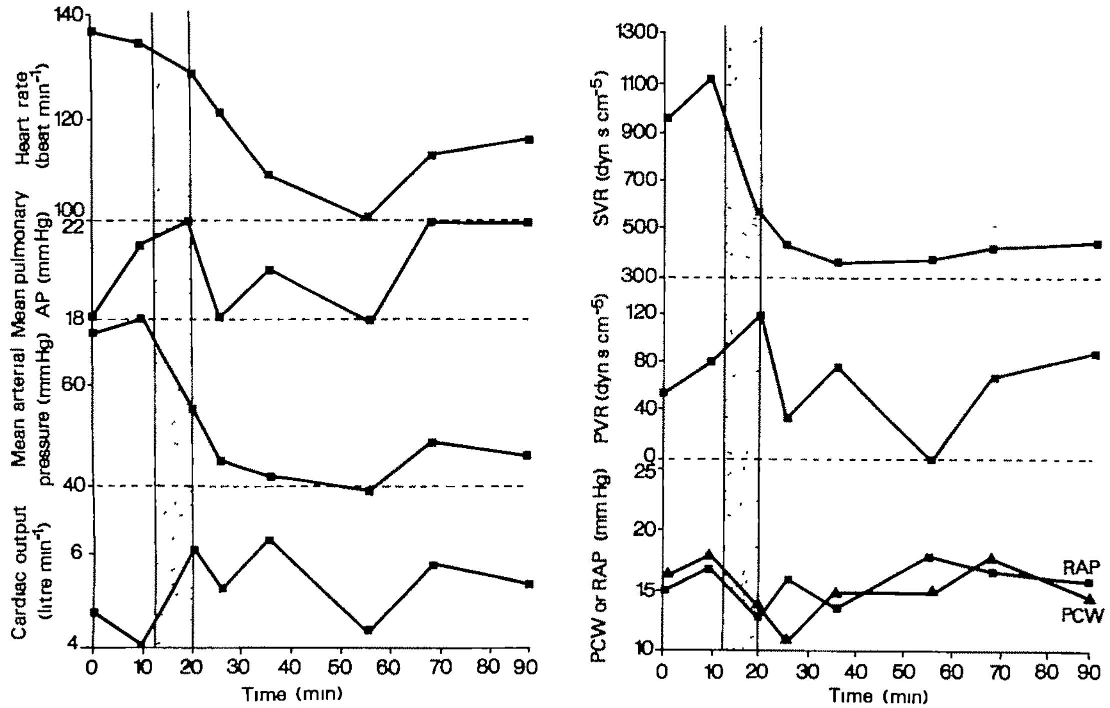

FIG. 1. Changes in cardiovascular variables following release of increased intra-abdominal pressure (Patient 1). The dotted area represents the time during which decompression occurred. Methoxamine and ephedrine were administered at 55 min. RAP = Right atrial pressure; PCW = pulmonary capillary wedge pressure; SVR = systemic vascular resistance; PVR = Pulmonary vascular resistance.

low, methoxamine 20 mg and ephedrine 30 mg were administered.

The measurements obtained are shown in figure 1. Heart rate decreased immediately after decompression. There was a decrease in MAP, but little change in MPAP. Both RAP and PCWP decreased initially after decompression but then increased to their baseline values. There was a prompt increase in CO and PVR, and a decrease in SVR. Following treatment with methoxamine and ephedrine, MAP increased slightly, accompanied by an increase in CO; SVR remained low.

Patients 2 and 3

Two other patients underwent orthotopic liver transplantation for sclerosing cholangitis and continued to bleed in the postoperative period. The details of all three patients are compared in table I. Patients 2 and 3 also required massive blood transfusion after their transplant surgery, to replace blood lost via abdominal drains and into the abdominal cavity. Both underwent laparotomy for decompression of abdominal tamponade, one

TABLE I. *Details of the three patients who underwent laparotomy for release of abdominal tamponade on four occasions.* **Additional external blood loss through intra-abdominal drains. HAS = Human albumin solution; FFP = fresh frozen plasma*

	Patient 1	Patient 2	Patient 3	
			a	b
Age (yr)	35	25	33	
Sex	M	M	M	
Weight (kg)	62	55	62	
Transfusion requirement between operations				
FFP (ml)	1000	3500	1250	1000
Platelets (units)	6	6	12	6
Blood (litre)	13.6	22.4	14.7	16.2
HAS (ml)	1600	0	8000	1200
Time between operations (h)	8	20	37	26
Tamponade volume* (litre)	6	9	11	7

patient on two occasions (3a and 3b). Morphine and midazolam, administered for analgesia and sedation on the Intensive Care Unit were continued up to the time of surgery at a dose of 3–5 mg h^{-1} for each agent. A period of stabilization was allowed after the induction of anaesthesia (with fentanyl 50 μg and ketamine 100 mg). No neuromuscular blocking agents were administered. On account of the results of the intensive intraoperative monitoring of the first patient, these patients were monitored using the same techniques and rapid blood transfusion was withheld. Peak airway pressures were also noted and arterial blood was sampled at intervals for estimation of oxygen and carbon dioxide tensions, and electrolyte concentrations. In one patient, end-tidal carbon dioxide concentration (E'_{CO_2}) was monitored, together with core and peripheral temperatures using temperature probes in the nasopharynx and on the foot. Haemodynamic measurements were made frequently throughout the perioperative period.

The haemodynamic measurements made before and after the decompression in patients 2 and 3 are shown in table II. Heart rate decreased on all occasions, as did mean arterial pressure; there was an increase in CO and a sharp decrease in SVR. Patient 3, during his first laparotomy (3a), was able

TABLE II. *Haemodynamic changes seen before, and after, decompression of abdominal tamponade in patients 2 and 3. HR = Heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; RAP = right atrial pressure (mean); PCWP = pulmonary capillary wedge pressure; CO = cardiac output, SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; CT = core temperature; PT = peripheral temperature;* E'_{CO_2} *= end tidal carbon dioxide concentration*

	Patient	Before decompression	After decompression
HR (beat min^{-1})	2	120	107
	3a	120	110
	3b	111	109
MAP (mm Hg)	2	76	35
	3a	69	67
	3b	59	38
MPAP (mm Hg)	2	31	15
	3a	25	25
	3b	36	19
RAP (mm Hg)	2	23	12
	3a	14	17
	3b	20	10
PCWP (mm Hg)	2	32	18
	3a	19	17
	3b	22	10
CO (litre min^{-1})	2	3.6	4.9
	3a	7.4	10.2
	3b	10.3	12.2
SVR (dyn s cm^{-5})	2	1177	376
	3a	594	392
	3b	302	183
PVR (dyn s cm^{-5})	2	160	93
	3a	65	63
	3b	108	59
CT (°C)	3b	37.0	36.7
PT (°C)	3b	28.8	30.7
E'_{CO_2} (%)	3b	5.6	7.2

TABLE III. *Changes in some of the cardiovascular variables following intra-operative administration of various sympathomimetic agents in patients* 2 *and* 3. *HR = Heart rate; MAP = mean arterial pressure; CO = cardiac output; SVR = systemic vascular resistance. b = Bolus; i = infusion;* * *not noted*

	Patient	Before methoxamine	After methoxamine	Before ephedrine	After ephedrine	Before vasopressin	After vasopressin	Before adrenaline	After adrenaline
Dose	2					10 u.		b 0.3 mg	
								i 4.0 mg h^{-1}	
	3a	10 mg		15 mg					
	3b	20 mg				7 u.		b 0.3 mg	
						10 u.		i *	
HR (beat min^{-1})	2					107	120	b 120	b 127
								i 127	i 137
	3a	109	111	109	133				
	3b	102	100			126	115	b 100	b 82
						111	101	i 110	i 111
MAP (mm Hg)	2					35	44	b 44	b 53
								i 53	i 57
	3a	56	58	48	60				
	3b	44	51			65	87	b 51	b 107
						45	67	i 48	i 74
CO (litre min^{-1})	2					4.9	3.9	b 3.9	b 4.1
								i 4.1	i 2.5
	3a	9.7	11.7	11.4	13.6				
	3b	10.3	9.9			12.9	11.3	b 9.9	b 10.0
						10.6	9.7	i 10.9	i 12.9
SVR (dyn s cm^{-5})	2					376	533	b 533	b 839
								i 839	i 1560
	3a	338	267	231	282				
	3b	264	307			285	446	b 307	b 728
						294	395	i 300	i 378

to maintain cardiovascular stability better than on the subsequent occasion; MAP was maintained by a considerable increase in CO. During decompression, core temperature decreased slightly while the temperature on the foot increased by 2 °C. There were marked increases in hydrogen ion concentration, Pa_{CO_2} and E'_{CO_2}, and a smaller increase in potassium concentration. There was no consistent change in Pa_{O_2} or in ionized calcium or sodium concentrations.

The responses of HR, MAP, CO and SVR of patients 2 and 3 to different sympathomimetic agents are shown in table III. Methoxamine had no effect on MAP, CO or SVR. However, ephedrine increased MAP slightly by increasing CO. Vasopressin increased MAP to a greater extent and in a more appropriate way by increasing SVR, but a greater increase in SVR was seen with the bolus administration of adrenaline. There was no evidence of an additive effect between the various agents administered.

DISCUSSION

The immediate haemodynamic changes seen following the release of increased intra-abdominal pressure have not been described previously. Richards and colleagues (1983) described the haemodynamic changes in three patients before, and after, the release of abdominal tamponade—but over a longer time course and not during the operation. They observed decreases in mean arterial pressure, central venous pressure and pulmonary capillary wedge pressure after decompression, but little alteration in cardiac output or total peripheral resistance. Other studies on increased intra-abdominal pressure have been in patients undergoing laparoscopy (Kelman et al., 1972; Lewis et al., 1972). These have produced less comprehensive, and conflicting, results which appear to be dependent on the intra-abdominal pressure (Motew et al., 1973).

Studies in dogs have described the changes seen with increasing intra-abdominal pressure (Richardson and Trinkle, 1976; Toomasian, 1978; Kashtan et al., 1981): cardiac output decreased and total peripheral resistance increased with increasing intra-abdominal pressure. This effect was most marked in dogs rendered hypovolaemic. The reduction in cardiac output was thought to reflect not only an increased peripheral resistance, but also myocardial depression and a decrease in venous return. Alterations in pleural pressure with increased intra-abdominal pressure were insignificant and thought not to contribute to the haemodynamic changes.

The variability in cardiovascular indices observed in man may be the result of different degrees of arterial compression, of cardiovascular instability at the time, and of the concurrent treatment of this instability. The latter factors were minimized as far as possible while these patients were studied. Although intra-abdominal pressure was not measured, these patients appear to have had arterial compression as well as venous occlusion in the splanchnic and lower limb vessels. The increases in temperature at the foot, and in Pa_{CO_2}, E'_{CO_2} and hydrogen ion and potassium concentrations on decompression are evidence of re-established distal circulation following arterial compression. The increase in E'_{CO_2} has been noted previously in similar patients (J. V. Farman, personal communication).

Before abdominal decompression, MAP was maintained by blood transfusion; all patients had a tachycardia and RAP and PCWP were increased. Patients 1 and 2 had a reduced CO and normal SVR, but patient 3 had an increased CO, with a low SVR. All three patients had a low PVR but high MPAP.

Following abdominal decompression, there was an immediate increase in CO which was associated with a decrease in heart rate and an increase in stroke volume. There was a sharp decrease in SVR. Since the increase in CO was smaller than the decrease in SVR, MAP decreased, and since the main cause of the hypotension was a low SVR, vasconstrictors were the most appropriate form of treatment.

Sympathomimetic agents were relatively ineffective in increasing SVR. Methoxamine had no effect and ephedrine, although it increased MAP, did so by increasing CO, SVR remaining low. Vasopressin is an endogenous vasoconstrictor with an important action on the splanchnic vascular bed. In these patients, it caused an increase in MAP by increasing SVR. Adrenaline, which also causes splanchnic vasoconstriction, increased MAP by increasing SVR when given by bolus administration. When given by infusion, adrenaline again increased SVR, and in patient 2 this was sufficient to decrease CO so that MAP did not increase. Vascular pooling may also occur as a result of vasodilatation of the splanchnic circulation and loss of tone of the intestinal smooth muscles—the latter occurring because of hypoxia resulting from the increased intra-abdominal pressure in these patients. The action of adrenaline is complex and may depend upon smooth muscle tone (Weiner, 1985). Intensive monitoring is, therefore, advisable during its administration, particularly in this situation.

The haemodynamic changes described following abdominal decompression are compatible with the release of a high intra-abdominal pressure and the re-establishment of splanchnic and lower limb circulation. The splanchnic venous system is known to be an important blood reservoir (Greenaway, 1983) and maximal dilatation of these vessels would produce a system with a large capacity. Constriction of the splanchnic vasculature is mediated by alpha-adrenoceptors (Corday and Williams, 1960; Hirsch and Rone, 1982). These patients, however, responded poorly to sympathomimetic agents and required large doses of endogenous vasoconstrictors with a specific effect on the splanchnic circulation. This may be because of the presence of an abnormal circulation with maximally dilated vessels unresponsive to normal doses of sympathomimetic agents. This, in turn, may be a mechanical problem, with the vessels splinted open by fibrous adhesions formed as a result of the patient's original pathology, or it may be that the alpha-adrenoceptors are poorly responsive, possibly on account of the release of vasoactive substances or toxins produced during tamponade. Chernow (1985) has postulated this type of mechanism based on a theory described by Berridge and Irvine (1984) and future pharmacological developments in alpha-receptor modulators may elucidate its importance.

Although all these patients died eventually, none died with the ventilatory complications, seen previously in similar patients, which may have been the result of overtransfusion. Two further patients have been managed along the lines described above. The data on these patients are incomplete, but both survived to be discharged from the Intensive Care Unit and, in particular, neither had pulmonary complications resulting from fluid overload. The frequent pulmonary complications previously seen in these patients may have been the result of inappropriate treatment of hypotension with excessive blood transfusion following abdominal decompression. Although some volume replacement is necessary during such operations, vasoconstrictors may be required in addition.

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CORRESPONDENCE

COMPARISON OF PRESSURES MEASURED FROM THE PROXIMAL EXTERNAL JUGULAR VEIN AND FROM A CENTRAL VEIN

Sir,—The study by Shah, Swai and Latto (1986) comparing the venous pressures measured from the proximal external jugular vein and from a central vein was interesting. The authors found a mean difference in pressure of 3 mm Hg from the two sites which was not influenced by alterations in the head position or the side of jugular venous catheterization.

Whether the reference zero is the right atrium or manubriosternal joint, the manometer scale or transducer must bear a constant relation to the zero (Lawler, 1980). The scale or transducer should be fixed to the patient or the operating table, rather than to a freestanding pole. The authors have failed to mention the position of the transducer in relation to the zero point. As the measurements were taken in the horizontal position, one is compelled to believe that the transducer was at the body level. Although a source of error did exist, it was probably equal for all the measurements. As long as the body position is horizontal, the measurement from a slightly distant vein like proximal external jugular may reflect near true venous pressures, as the authors have found. This is not necessarily true if the patient is tilted or slightly head-up on the operating table or intensive care bed. Then the position of the transducer becomes more important. Moreover, changes in the central venous pressure are more important than a single value, particularly after fluid challenge.

It remains to be seen what the effects of posture and fluid challenge would be on the pressures measured from the proximal external jugular vein and a central vein.

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Shah, M. V., Swai, E. A., and Latto, I. P. (1986). Comparison between pressures measured from the proximal external jugular vein and a central vein. *Br. J Anaesth.*, **58**, 1384.

Sir,—We would like to thank Dr Kumar for his interest in our study and for his comments related to it.

We used the manubriosternal joint as the reference zero, with the transducer fixed to a free standing pole. The patient was at the same horizontal level and the transducer had a constant relationship to the reference zero throughout the study period. As the title suggests, our study compared the pressures from the external jugular vein and from a reliably placed central venous line using this reference zero. We therefore fail to understand his contention that a source of error did exist in our measurements.

We are entirely in agreement with his observation that pressures from the external jugular vein will be influenced by patient position. If the patient is placed in the head-up or head-down position, an allowance will need to be made for the hydrostatic pressure difference between the reference zero and the tip of the catheter in the external jugular vein. Indeed, adjustments may need to be made to central venous pressure measurements with changes in the patient's position if the reference zero is the manubriosternal joint.

Measurement of the external jugular venous pressures and central venous pressure in response to a fluid challenge or changes in blood volume were not formally investigated in our cardiac patients, for obvious clinical reasons. However, the measurements in our study correlated over a wide range of pressures. Also the pressures from the two catheters during the course of cardiac anaesthesia were similar when measured.

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I. P. Latto
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IN VITRO DEGRADATION OF ATRACURIUM IN HUMAN PLASMA

Sir,—The experiments reported by Stiller, Cook and Chakravorti (1985) confirm our earliest conclusions (Coker et al., 1981; Stenlake et al., 1981) that the particular structural features of atracurium enable the mutual promotion of Hofmann elimination and enzymic ester hydrolysis, in which the ester carbonyl groups facilitate Hofmann degradation and the quaternary ammonium groups enhance ester hydrolysis.

Thus, we observed about 70% decrease in potency in cats given atracurium which had been incubated for 30 min at 37 °C in pH 7.4 buffer, compared with unincubated atracurium in water acidified to pH 3.0. This finding was supported by the, as then, unpublished work of Merrett, Thompson and Webb (1983) in which potency measurements in mice, following incubation of atracurium with appropriate buffers, showed that it undergoes a non-enzymic decomposition four times faster at pH 7.6 and 10 times faster at pH 8.0 than at pH 6.9.

Such sensitivity to decomposition at mildly alkaline pH is uncharacteristic of chemically-mediated ester hydrolysis, but typical of Hofmann elimination. Accordingly, as we commented at the time, the extensive breakdown of atracurium in buffer at pH 7.4 (70% in 30 min) rightly contrasts sharply with that of suxamethonium, which is incapable of Hofmann elimination and only 6% hydrolysed in 1 h in buffer at that pH, and no more than 12% hydrolysed in the same time at pH 7.7 (Goedde, Held and Atland, 1968). For this reason, whilst none of these experiments or the other supporting experiments reported in the same paper and elsewhere (Hughes and Chapple, 1981) distinguish unequivocally between the two breakdown reactions, we hold firmly to the view that Hofmann elimination is the predominant factor in the underlying chemical breakdown of atracurium *in vivo*.

We also found that atracurium was less stable in human plasma than in buffer—an observation supported by the later work of Merrett, Thompson and Webb (1983) which showed that the rate of decomposition in human plasma was twice as rapid as that in buffer at the same pH. We concluded that this was the result of an enzyme-catalysed hydrolysis, but went on to show, by comparison with other atracurium-related compounds, that degradation was also dependent on the integrity of the Hofmann capability (Stenlake et al., 1981, table IV). This is especially relevant, as two of the primary breakdown products (quaternary alcohol and quaternary monoacrylate) are themselves capable of further degradation by both Hofmann elimination and ester hydrolysis. It is also relevant that the esterase mechanism for atracurium, in contrast to that for suxamethonium, is not dependent on pseudocholinesterase activity, and it is significant that throughout its extensive clinical use there have been no reports on atracurium of the prolonged paralysis and apnoea seen with suxamethonium in patients with pseudocholinesterase deficiency or with a typical plasma esterases.

We also reported and commented upon the biphasic pattern of release of ^{14}C-laudanosine from ^{14}C-atracurium iodide in reconstituted, pooled, dried human plasma, fresh human plasma, fresh whole blood and atypical human plasma with a 65% deficiency of pseudocholinesterase. There are differences between the present study and our own in methodology, atracurium salt, and the pH of the plasma samples used, and in the overall rates of laudanosine release. Nevertheless, the same pattern of an initial fast release of about 50% of the available laudanosine with subsequent slowing was very clearly demonstrated by us with all the above mentioned substrates. We still hold to the view expressed in our comment at the time, that "the sharp change in the slope of the curve is consistent with an initial fast Hofmann elimination of the intact ester accompanied by ester hydrolysis, with a reduction in the elimination rate as the quaternary acid is formed". This conclusion rests on accepted theoretical grounds that replacement of the powerful electron-withdrawing ester group (COOR), which is the key to activation of the Hofmann elimination in atracurium, by the significantly less powerful electron-withdrawing carboxyl (COOH) group of the quaternary acid will necessarily slow the elimination reaction. We would add, however, in the context of the present debate, that whilst there is no experimental evidence to support the view, there is every reason to suppose that the rates of ester hydrolysis of the quaternary monoacrylate and the quaternary alcohol are unlikely to be greatly different from that of atracurium itself, since all three contain the same structurally identical quaternary ammonium-ester function.

We therefore agree with the comments of Stiller, Cook and Chakravorti (1985) that the breakdown of atracurium in human plasma does not occur simply by two completely separate pathways. Furthermore, we submit, in extension of their conclusions, that the complete release of 2 molecules of laudanosine can only be rationalized on the basis of a fully integrated network of Hofmann eliminations and ester hydrolyses embracing atracurium and all its metabolites, as was clearly envisaged in our original publication (Stenlake et al., 1981, Scheme 3). For this reason we consider that the statement "we estimate that at 40 min, two thirds of atracurium is degraded by ester hydrolysis and one third by Hofmann elimination" by Dr Stiller and his colleagues is capable of misinterpretation—even more so when, from our reading of the graphical evidence presented (the precise mole ratio at 40 min is omitted from the table), significantly more than 1 mol of laudanosine (*ca* 1.2 mol) is released per mole of atracurium in that time.

The existence of ester degradation in measurable amounts in human plasma does not detract from the fact that the unique method of decomposition of atracurium, by Hofmann elimination, is responsible for the constant response in all pathological states including renal and hepatic failure (Ward and Neill, 1983), pseudocholinesterase deficiency (Baraka and Jaude, 1984) and in at least one case of organophosphorus poisoning (Baraka, Cava and Jaoude, 1984) where the cholinesterases are inhibited. Although, as yet, it has not been possible to quantify the relative contribution of Hofmann elimination *in vivo*, there is ample evidence that it plays a major role in the degradation of atracurium in man.

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INFUSION OF ALFENTANIL OR PETHIDINE FOR SEDATION OF VENTILATED PATIENTS IN THE ITU

SIR,—I would like to comment on the article by Yate and colleagues published in your October 1986 issue. The authors conclude by saying that "Alfentanil at an infusion rate of 0.4–0.5 μg kg^{-1} min^{-1} can be used as the main agent for sedation of ventilated patients in the I.T.U." I would like to raise the following points.

It must be appreciated that one cannot apply the results obtained in this paper to all ventilated patients requiring sedation in the I.T.U. All patients studied were post-cardiac by-pass, they had received a mixture of opiates (papaveretum 15–20 mg, fentanyl 1 mg, and alfentanil infusion), promethazine, a long acting anti-histamine (with a documented duration of action of 12 h, and a sedative effect stronger than chlorpromazine) and a benzodiazepine with a half-life of more than 22 h—lorazepam.

This polypharmacy alone makes it difficult to apply the results obtained in such a homogeneous group to the heterogeneous group of patients dealt with in the I.T.U.

My experience of using alfentanil as a main sedative agent combined with regular midazolam or diazepam, has shown that some patients may require alfentanil 1.6 μg kg^{-1} min^{-1} to produce satisfactory sedation. The delayed ventilatory depression experienced with alfentanil at much lower rates of infusion, which was highlighted in this study, alerts us to possible complications with more frail patients who may require sedation.

In summary, I feel that the optimism expressed by Yate and colleagues must be carefully reviewed using a broader patient population before one can support its use as a main agent for sedation of ventilated patients in the I.T.U.

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REFERENCE

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ABNORMAL ALFENTANIL PHARMACOKINETICS

Sir,—In a recently published study of alfentanil pharmacokinetics during prolonged infusion in the intensive care unit (Yate et al., 1986) we described one patient who demonstrated grossly abnormal alfentanil kinetics. The kinetics in this patient (patient No. 15 in the paper) were an elimination half-life of 720 min, a volume of distribution of 0.6 litre kg^{-1} and an estimated clearance of 0.66 ml kg^{-1} min^{-1} after a dose of alfentanil 25 mg given over 17 h.

We have recently had the opportunity to restudy this patient as a volunteer. The patient, a 64-yr-old female weighing 55 kg, was given a single i.v. dose of alfentanil 700 μg. Venous blood samples were taken before the injection and then at 2, 5, 11, 15, 30, 60, 120, 180, 240, 300 and 360 min afterwards for estimation of plasma alfentanil concentrations—which were measured by radioimmunoassay. On this occasion the calculated kinetic variables were $T_{\frac{1}{2}}^{\alpha}$ 6.9 min, $T_{\frac{1}{2}}^{\beta}$ 161 min, V_D 458 ml kg^{-1} and clearance 1.96 ml kg^{-1} min^{-1}.

The elimination half-life found was at the upper end of the range normally quoted for alfentanil and was attributable to a low clearance rather than to an increase in the volume of distribution. The possibility of an identifiable group of patients with a prolonged elimination half-life of around 160 min has been previously suggested (McDonnell et al., 1982), and it may be that this patient belongs to this group.

We do not know the reason for the differences between the kinetics found this time and previously; however, there are various possibilities. The total dose administered on the first occasion was larger by a factor of 34 and it may be that, in this patient, alfentanil kinetics could be better described by a Michaelis–Menten model similar to that seen with high-dose thiopentone infusions (Stanski et al., 1980). Alternatively, after major surgery there would almost certainly be alterations in hepatic blood flow although, as alfentanil has a low hepatic extraction ratio, changes in liver blood flow should have little effect. As alfentanil excretion can be described as binding sensitive capacity limited, changes in protein binding could have a profound effect and alfentanil is bound to acute phase proteins which are known to increase after cardiac surgery.

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ACKNOWLEDGEMENT

We are grateful to Dr Robert Woestenborghs for performing the alfentanil assay.

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SPINAL NEEDLES, GAUGE AND HEADACHE

Sir,—Gauge standards evolved before the international metric system. British Imperial Standard Wire Gauge (SWG) became a legal standard in England in 1883 (Camm, 1965). Some gauge standards are based on successive doubling or halving of an initial diameter, while others are multiplies of unknown origin. Certain standards have survived as measurements for thickness of needles. Without referring to which standard is used, the gauge concept is very inaccurate. To demonstrate this inaccuracy, we have examined needles supplied for dural puncture from two companies: Braun (German) and Becton & Dickinson (British). From both companies 25-gauge needles are orange, 26-gauge needles are brown, without reference to the gauge standards used. Macroscopically, one can easily see and feel differences in the thicknesses of the needles.

A total of 40 needles were examined: 10 needles of each size (25-gauge and 26-gauge) from Braun (Spinocan), and 10 of each from Becton & Dickinson. The examination was performed by the State Institute of Technology in Oslo. The thickness of the needles was measured with length-measuring equipment SIP MUL-1000 connected to a laser measuring system HP 55 28 A. The maximum and minimum diameter

TABLE I. *Diameters of needles from Braun and Becton & Dickinson*

	Braun		Becton & Dickinson	
Diameter (mm)	25-gauge (orange)	26-gauge (brown)	25-gauge (orange)	26-gauge (brown)
Maximum	0.5675	0.4608	0.5207	0.4718
Minimum	0.5536	0.4550	0.5113	0.4606

TABLE II. *Reference dimensions of nominal diameters for U.S. Standard and Standard Wire Gauge*

Size in gauge	Nominal diameter (mm) U.S. Standard	Nominal diameter (mm) Standard Wire Gauge
25-gauge	0.556	0.508
26-gauge	0.476	0.457

anywhere along each needle were found. The measuring precision was 10^{-4} mm The results are shown in table I. The maximum diameter of 25-gauge needles from Braun could be 0.0468 mm larger than the needles from B & D (9%). For the 26-gauge needles, those from B & D could have a maximum diameter 0.011 mm greater than those from Braun (2.4%).

The two companies (Braun and Becton & Dickinson) follow two different gauge standards. Braun follows U.S. standard, while B&D follows SWG. The nominal diameters in millimetres (mm) for the two standards are shown in table II. Comparing the measured diameters (table I) with the standards (table II), it is evident that Braun's 25-gauge and 26-gauge needles both fulfil the criteria for the U.S. standard. Likewise, B&D needles fulfil the criteria for 25-gauge and 26-gauge according to the SWG On the other hand, Braun 25-gauge needles do not fulfil the SWG standard; indeed, they are close to the 24-gauge SWG. Therefore, the incidence of headache after spinal anaesthesia may well differ depending on the actual needle (of the same nominal size) used.

Our investigation demonstrates how unprecise the gauge concept is. We recommend a change from gauge to millimetres for sizes of needles used in medicine.

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GUIDELINES FOR PATIENTS RECEIVING LITHIUM TREATMENT WHO REQUIRE MAJOR SURGERY

SIR,—One person out of every 1000 in the general population is receiving long-term prophylactic treatment with lithium for recurrent manic–depressive illness. When such patients require surgical intervention it is important that the anaesthetist is aware of the attendant risks and can take the appropriate precautions. We wish to draw attention to a few points which, we believe, are particularly relevant.

Discontinuation of lithium in connection with major surgery. Lithium is eliminated through the kidneys. A decrease in glomerular filtration rate, or a negative fluid and/or sodium balance may lead to a reduction in the renal clearance of lithium with resultant accummulation of lithium and risk of lithium poisoning. Lithium poisoning is dangerous and has, occasionally, led to death. Lithium treatment should, therefore, be discontinued 2–3 days before major surgery (the elimination half-life of lithium is about 24 h), and it should not be resumed until renal function and fluid–electrolyte balance are again normal. The treatment need not be discontinued for minor surgery. There is no clinical evidence of interaction between lithium and anaesthesic agents, although lithium may prolong the action of neuromuscular blocking drugs.

Resumption of lithium treatment. Prophylactic lithium treatment effectively prevents manic and depressive relapses. Discontinuation of the treatment involves risk of recurrences, sometimes with catastrophic results. It is, therefore, important that the interruption of lithium treatment—in connection with major surgery—is as short as possible. Difficulties arise if the lithium treatment is not restarted again after the surgery. This is illustrated by the following case history.

A female patient with a history of several severe depressions and one episode of mania started prophylactic lithium in 1974 and on this treatment remained free of episodes for 8 years. In 1982 lithium was discontinued because the patient had to undergo hip-joint surgery. Ten days later the patient became restless and tense and she herself suggested that the lithium treatment should be resumed. This was, however, disregarded, the intensity of the mania increased, and 5 weeks after the operation the patient had to be admitted to the closed ward of a psychiatric Unit. She was then violently manic, dysphoric, irritable and aggressive, and she lacked insight completely. Treatment with neuroleptic agents brought her mania under control, and lithium maintenance treatment was resumed. The patient has been free of symptoms since then.

Preoperative parenteral fluid administration. In some patients lithium treatment decreases the renal concentrating ability, with consequent development of polyuria and polydipsia These side effects may be troublesome for the patient, but they do not decrease the elimination of lithium and are not in themselves dangerous. However, owing to the reduced concentrating ability these patients become dehydrated rapidly if fluid intake is restricted or additional fluid lost. Dehydration may reduce the lithium clearance and increase the risk of lithium poisoning. If patients with lithium-induced polyuria must abstain from drinking before surgery, they should be given parenteral fluids the night before the operation. This point is illustrated by the following case history.

A female patient developed pronounced polyuria and polydipsia during lithium treatment, but decided that she could live with these side effects, because the treatment removed her manic and depressive episodes very effectively. She was, however, admitted to a surgical ward for uterine curettage and was forbidden food and fluid intake during the night before the operation. Under this regimen she developed symptoms of dehydration and slight lithium poisoning with malaise, hand tremor and dysarthria. When she was admitted for another curettage 1 year later, she protested against being deprived of fluid before anaesthesia, but the nursing staff clearly felt that this insistence on having something to drink was merely the whim of a psychiatric patient. Finally, she screamed so loudly that a psychiatrist was brought in, and he advised the administration of fluid i.v. before anaesthesia. In this way the patient avoided symptoms of dehydration and lithium poisoning.

Parenteral fluid administration may also be required for lithium-treated patients who vomit copiously, or who are unconscious for many hours.

In summary:

(1) Lithium should be discontinued 2–3 days before major surgery.

(2) The treatment should be resumed as soon as possible after the operation—that is, when kidney function and fluid–electrolyte balance have become normal.

(3) Patients with lithium-induced polyuria should be given fluids parenterally during the night before an operation, when they vomit copiously, or if they are unconscious for several hours.

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POTENCY RATIO BETWEEN OPIOID AGONISTS AND PARTIAL AGONISTS

Sir,—The paper by Klepper and colleagues (1986) again seems to indicate the belief of this group of workers in a fixed potency ratio between opioid agonists and partial agonists, although such a concept is theoretically unlikely (Kay, 1985). Support for a variable potency ratio is apparent in their paper, however, in that nalbuphine in so-called "equipotent" doses smaller than those in the range (8–10 mg) where equipotency has been demonstrated (Beaver and Feise, 1978) produced a greater effect than morphine. This observation correlates with the theoretical prediction based on nalbuphine having a flatter dose–response relation than morphine, as does the observation that doses of nalbuphine in excess of 10 mg produced less effect than "equipotent" doses of morphine. The paper confirms that nalbuphine has a flatter dose–response relation than morphine, and that a ceiling effect, or even reversal of effect, occurs. With non-parallel dose–response relations, any potency ratio between nalbuphine and morphine can only apply at a single dose.

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Klepper, I. D., Rosen, M., Vickers, M. D., and Mapleson, W. W. (1986). Respiratory function following nalbuphine and morphine in anaesthetized man. *Br. J. Anaesth.*, 58, 625.

Sir,—Dr Kay has previously made the point about fixed potency ratios (Kay, 1985). He is technically correct that, if the dose–effect curves are not parallel, use of a single potency ratio is inaccurate, but it is also true that the term potency is imprecise in a clinical context in which the end-point cannot be measured accurately, such as with an analgesic drug. Nevertheless, a single ratio is an approximation widely used to compare drugs in their clinical dose range. This rarely gives rise to a problem because any inaccuracy is swamped by the biological variation in dose between patients; from studies by patient-controlled analgesia this variation can range up to 10 times. Therefore, our comparison of doses of nalbuphine (4.4–50 mg/70 kg) and morphine (3–17.5 mg/70 kg) covers the range of doses used in clinical practice. Our work confirms that, unlike morphine, nalbuphine with increasing dosage causes limited ventilatory depression. That should be useful information for the clinician, whatever the definition of equipotency.

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BOOK REVIEWS

Basics of Anesthesia. By R. K. Stoelting and R. D. Miller. Published by Churchill Livingstone. Pp. 499; indexed; illustrated. Price £27.00.

In their preface, the authors say that this book "is intended to provide the student and beginning trainee with introductory information pertinent to the wide spectrum (operating room, intensive care, pain management, cardiopulmonary resuscitation) of the practice of anesthesiology". The breadth of approach is reflected in its 34 chapters, which also include a section on the pharmacology of drugs used in anaesthesia and a brief outline of anaesthetic history. It is strongly bound with clear print, good illustrations and a comprehensive index.

The book is very much an American work and no drugs or pieces of equipment other than those used in the U.S.A. are considered. A limited number of references designed to direct the reader to important or more detailed articles is given at the end of each chapter. This is a sound idea which allows the text to be read without interruption. However, more than 90% of them are from American publications and, because of this, several excellent sources have been omitted.

The authors have obviously set themselves a difficult task in attempting to introduce such a variety of topics (each of which in itself is potentially the subject of a specialist textbook) to the tyro anaesthetist. In the main they have succeeded well, and some sections are excellent. The necessary brevity and condensation of information does, however, on occasions lead to a rather didactic over-simplification of reality. For instance, lumbar sympathetic blockade (p. 196) is described as a straightforward, easy procedure with no mention of its potential complications or requirements for x-ray control and, when discussing spinal and general anaesthesia (p. 167), the authors give the impression that general and regional techniques are only ever combined when the latter has failed. There are also several basic sins of both omission and commission. For example, bronchospasm and pneumothorax are omitted from a discussion of complications which can occur while a tracheal tube is in place (p. 164), and the myth is perpetuated that the pressure in a nitrous oxide cylinder stays constant during use until all the liquid has evaporated (p. 130). Perhaps the most obvious error of all is the claim that Sir James Y. Simpson gave chloroform to Queen Victoria (p. 1).

Despite these criticisms, the book has much to offer a junior anaesthetic trainee—although because of its unashamedly American approach the majority of British graduates will, I suspect, prefer the British equivalents. It is, however, not a text to be ignored and could well be worth dipping into whilst studying for postgraduate examinations—when the Anglo-Saxon tomes can be faced no longer.

P. Hutton

Cholinesterase: Monographs in Human Genetics, Vol. 11. By M. Whittaker. Published (1986) by S. Karger, Basel. Pp. 134; indexed; illustrated. Price SFr. 130; DM 156; U.S. $ 55.50; £40.70.

This slim book is destined to become a classic. It is a monograph written by one of the acknowledged world authorities on the enzyme. Although short, the book covers all aspects of cholinesterase from chemical properties to ethnic distribution of the genotypes. The chapter on Cholinesterase in Clinical Medicine is particularly relevant to anaesthetists. In spite of citing over 500 references in 97 pages of text, the author manages to convey her opinions on the validity of some of the published data and points out areas for further study.

Unfortunately, the cost of this book will deter many potential purchasers. However, any anaesthetic department with a particular interest in cholinesterase or, more importantly, undertaking research on this enzyme, must have access to a copy It represents the knowledge and wisdom accumulated after 25 years of research.

G. M. Hall

Acute Pain Management. Edited by M. J. Cousins and G. D. Phillips. Published by Churchill Livingstone, New York. Pp. 300, indexed; illustrated.

This is the latest addition (No. 8) to the *Clinics in Critical Care Medicine* series. Its coverage of the management of acute pain is comprehensive. Following an introductory chapter describing the development of the management of pain, the physiology of pain is discussed and the relationships between pain, anxiety and sleep are reviewed. The modification of the stress response which follows successful pain relief is discussed, although it is pointed out that there is little evidence to show that morbidity is reduced as a consequence. By far the best chapters in the book are those relating to the use of nerve blockade with local anaesthetic solutions in the extradural space or for intercostal block, and with opioids either intrathecally or extradurally The chapter from the Edinburgh group on the use of extradural local anaesthetics is particularly good. The importance of psychological management of the patient in pain is dealt with adequately. The importance of alterations in drug metabolism in the critically ill patient and the effects of these upon drug interactions are discussed. Finally, in a chapter entitled "Practical Decision Making" the Editors provide suggested treatment regimens for a number of categories of patient.

The definition of the "critically ill" patient becomes somewhat blurred in this book. Although the chapter describing drug interactions and the final chapter on practical management address themselves directly to patients in an intensive care unit, the majority of authors mention intensive care management only in passing. In the United Kingdom, many people tend to regard critical care medicine as applying only to patients admitted to an intensive care unit. However, the Editors have provided *their* definition, which extends to include patients in the postoperative recovery room, high dependency surgical or medical wards or the emergency admissions unit. In this context, the book is excellent in most parts, although one or two of the reviews are, inevitably, similar to those published elsewhere by the same authors The emphasis on nerve blockade should provide British anaesthetists involved in intensive care management with food for thought.

The book can be thoroughly recommended to anaesthetists of all grades, and its readership should not be confined to those with intensive care responsibilities.

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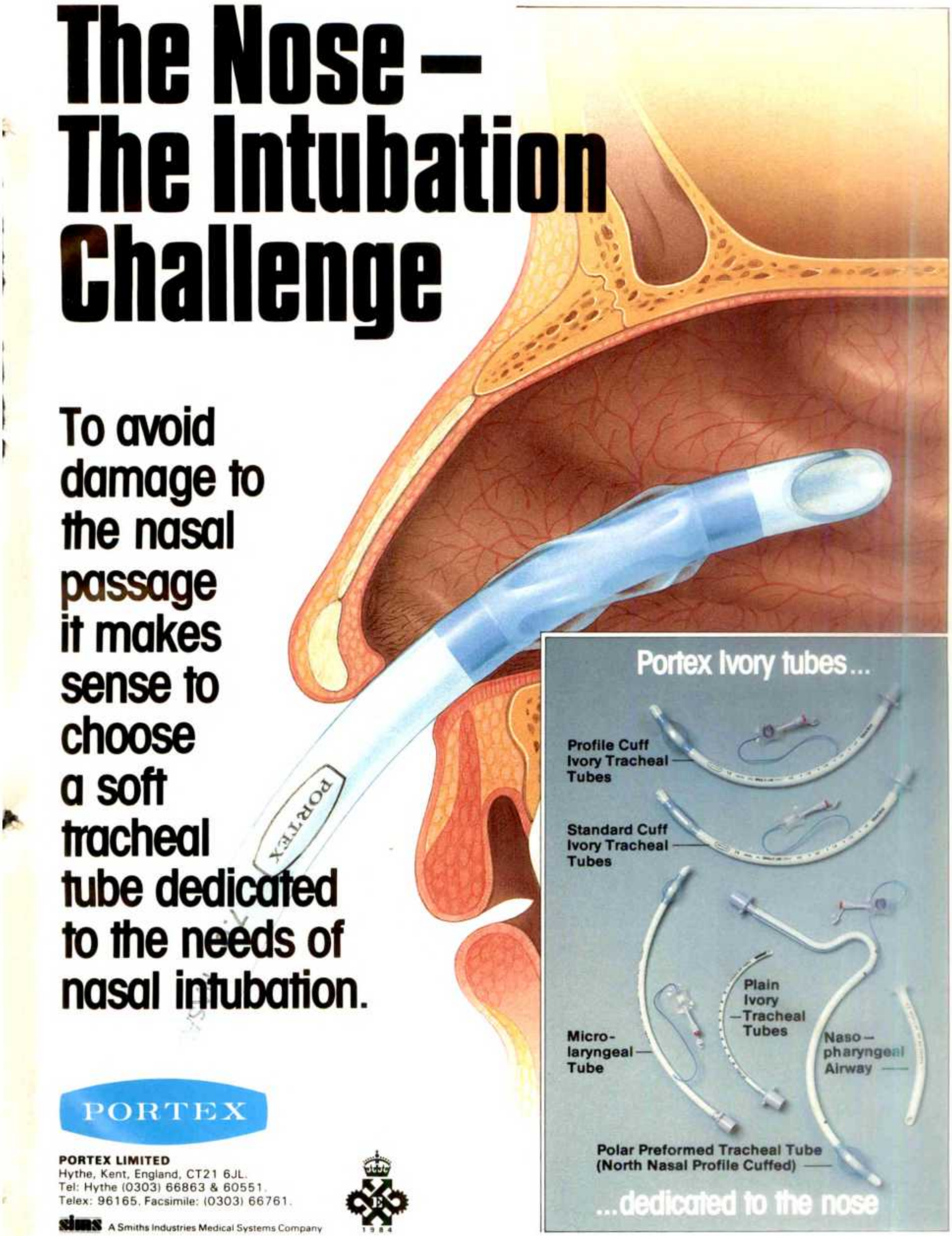

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